

Structural Effects on Stability and Reactivity

Introduction

The concepts of *stability* and *reactivity* are fundamental to understanding chemistry. In this chapter we consider first the *thermodynamic* definition of chemical stability. We then consider *chemical kinetics* (Section 3.2) and how it can provide information about reactivity. We also explore how structure influences stability and reactivity. We want to learn how to make predictions about reactivity based on the structure of the reactants and intermediates. We begin by reviewing the principles of thermodynamics and kinetics, which provide the basis for understanding the relationship of structure to stability and reactivity.

Reactions are usefully described in terms of potential energy diagrams such as shown in Figure 3.1, which identify the potential energy changes associated with the reacting molecules as they proceed to products. The diagram plots the free energy of the system as a function of the progress of the reaction. For each individual step in the reaction there is a *transition state* representing the highest energy arrangement of the molecules for that step. The successive *intermediates* are the molecules that are formed and then react further in the course of the overall reaction. The energies of the transition states relative to the reactants determine the rate of reaction. The energy difference between the reactants and products is ΔG , the free-energy change associated with the reaction. The free energy of a chemical reaction is defined by the equation

$$\Delta G = \Delta H - T\Delta S \quad (3.1)$$

where ΔH is the *enthalpy change* and ΔS is the *entropy change* for the reaction. The enthalpy term is a measure of the stability of the molecule and is determined by the strength of the chemical bonds in the structure. The entropy term specifies the change

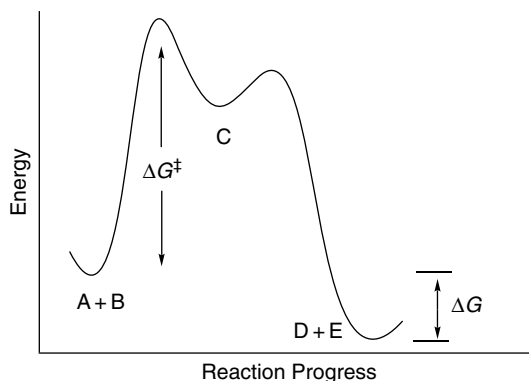


Fig. 3.1. Reaction potential energy profile showing transition states and intermediate for a reaction $A + B \rightarrow C \rightarrow D + E$.

in the order (probability) associated with the reaction. The *free energy* of the reaction, ΔG , determines the position of the equilibrium for the reaction:

$$\Delta G = -RT \ln K \quad (3.2)$$

where K is the equilibrium constant for the reaction:

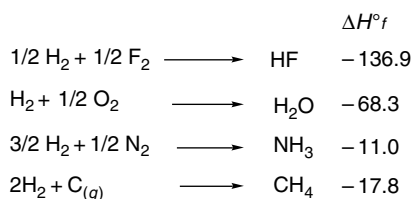
$$K = \frac{[D][E]}{[A][B]}$$

The energy required to proceed from reactants to products is ΔG^\ddagger , the *free energy of activation*, which is the energy at the transition state relative to the reactants. We develop the theoretical foundation for these ideas about reaction rates in Section 3.2. We first focus attention on the methods for evaluating the inherent thermodynamic stability of representative molecules. In Section 3.3, we consider general concepts that interrelate the thermodynamic and kinetic aspects of reactivity. In Section 3.4, we consider how substituents affect the stability of important intermediates, such as carbocations, carbanions, radicals, and carbonyl addition (tetrahedral) intermediates. In Section 3.5, we examine quantitative treatments of substituent effects. In the final sections of the chapter we consider catalysis and the effect of the solvent medium on reaction rates and mechanisms.

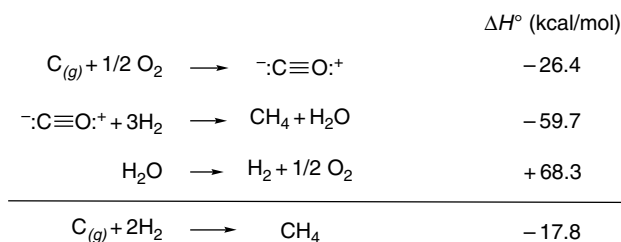
3.1. Thermodynamic Stability

Thermodynamic data provide an unambiguous measure of the stability of a particular compound under specified conditions. The thermodynamic measure of molecular stability is ΔH_f° , the *standard enthalpy of formation*, which gives the enthalpy of the compound relative to the reference state of its constituent elements under standard conditions of 1 atm and 298 K. For each element a particular form is assigned an enthalpy (potential energy content) of 0. For example, for hydrogen, nitrogen, oxygen, and fluorine, the gaseous diatomic molecules are the reference states. For carbon, 0 energy is assigned to graphite ($C_{(g)}$), which consists entirely of sp^2

carbon atoms. The ΔH_f° of compounds can be measured directly or indirectly. The ΔH_f° in kcal/mol of HF, H₂O, NH₃, and CH₄ are found to be as follows:



The ΔH_f° of a given compound is a physical constant and is independent of the process by which the compound is formed. Therefore, ΔH_f° values are additive and can be calculated precisely for balanced chemical equations if all the necessary data are available. For example, it might be experimentally impossible to measure the ΔH_f° of methane directly by calorimetry, but it can be calculated as the sum of the enthalpy for an equivalent reaction sequence, e.g.:



The ΔH_f° for many compounds has been determined experimentally and the data tabulated.¹ In the sections that follow, we discuss approaches to computing ΔH_f° when the experimental data are not available. It is important to note that direct comparison of the ΔH_f° values for nonisomeric compounds is not meaningful. The ΔH_f° for methane through hydrogen fluoride, for example, gives us no comparative information on stability, because the reference points are the individual elements. Other information is needed to examine relative stability. For example, as is discussed in the next section, it is possible to assign *bond energies* to the bonds in CH₄, NH₃, H₂O, and HF. This is the energy required to break a C–H, N–H, O–H, or H–F bond. These numbers do begin to provide some basis for comparison of the properties of nonisomeric compounds, as we now see that the X–H bonds become stronger as we go from C to F in the second-row compounds with hydrogen.

Compound	X–H bond energy (kcal/mol)
CH ₄	105.0
NH ₃	108.2
H ₂ O	119.3
HF	136.4

¹ J. B. Pedley, R. D. Naylor, and S. P. Kirby, *Thermochemical Data of Organic Compounds*, 2nd Edition, Chapman and Hall, London, 1986; H. Y. Afeefy, J. F. Liebman, and S. E. Stein, in *NIST Chemistry Webbook*, NIST Standard Reference Database Number 69, P. J. Linstrom and W. G. Mallard, eds., 2001 (<http://webbook.nist.gov>).

3.1.1. Relationship between Structure and Thermodynamic Stability for Hydrocarbons

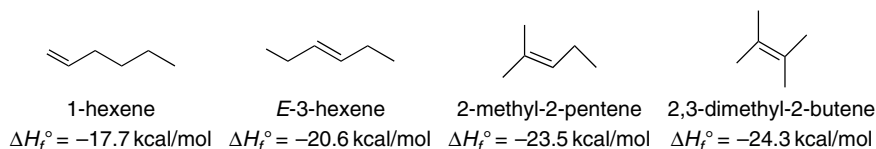
Extensive thermodynamic data are available for the major classes of hydrocarbons. Table 3.1 gives data for the C_4 – C_6 and C_8 alkanes and the C_4 – C_6 alkenes, and several general relationships become apparent. One is that *chain branching increases the stability of alkanes*. This relationship is clear, for example, in the data for the C_6 alkanes, with a total enthalpy difference of nearly 4 kcal/mol between the straight-chain hexane and the tetra-substituted 2,2-dimethylbutane. There is a similar range of 4.5 kcal/mol between the least stable (octane) and most stable

Table 3.1. Standard Enthalpy of Formation of Some Hydrocarbons (in kcal/mol)^a

Alkanes (liquid)			
C_4		C_8	
Butane	–35.0	Octane	–59.8
2-Methylpropane	–36.7	2-Methylheptane	–60.9
		3-Methylheptane	–60.3
		4-Methylheptane	–60.1
C_5		2,2-Dimethylhexane	–62.6
Pentane	–41.5	2,3-Dimethylhexane	–60.4
2-Methylbutane	–42.7	2,4-Dimethylhexane	–61.4
2,2-Dimethylpropane	–45.5	2,5-Dimethylhexane	–62.2
		3,4-Dimethylhexane	–60.2
C_6		3,3-Dimethylhexane	–61.5
Hexane	–47.5	2,2,3-Trimethylpentane	–61.4
2-Methylpentane	–48.9	2,2,4-Trimethylpentane	–62.0
3-Methylpentane	–48.4	2,3,4-Trimethylpentane	–60.9
2,3-Dimethylbutane	–49.6	2,3,3-Trimethylpentane	–60.6
2,2-Dimethylbutane	–51.1	3-Ethyl-2-methylpentane	–59.7
		3-Ethyl-3-methylpentane	–60.4
		2,2,3,3-Tetramethylbutane	–64.3
B. Alkenes (liquid)			
C_4		C_6	
1-Butene	–4.90	1-Hexene	–17.7
<i>E</i> -2-Butene	–7.89	<i>E</i> -2-Hexene	–20.4
<i>Z</i> -2-Butene	–7.10	<i>Z</i> -2-Hexene	–20.1
2-Methylpropene	–8.96	<i>E</i> -3-Hexene	–20.6
		<i>Z</i> -3-Hexene	–18.9
C_5		2-Methyl-1-pentene	–21.5
1-Pentene	–11.2	3-Methyl-1-pentene	–18.7
<i>E</i> -2-Pentene	–13.9	4-Methyl-1-pentene	–19.1
<i>Z</i> -2-Pentene	–12.8	2-Methyl-2-pentene	–23.5
2-Methyl-1-butene	–12.3	3-Methyl-2-pentene	–22.6
3-Methyl-1-butene	–16.4	<i>E</i> -3-Methyl-2-pentene	–22.6
		<i>Z</i> -3-Methyl-2-pentene	–22.6
		<i>E</i> -4-Methyl-2-pentene	–21.9
		<i>Z</i> -4-Methyl-2-pentene	–20.8
		2,3-Dimethyl-1-butene	–22.3
		3,3-Dimethyl-1-butene	–20.9
		2-Ethyl-1-butene	–20.8
		3,3-Dimethyl-1-butene	–20.9
		2,3-Dimethyl-2-butene	–24.3

a. From *Thermochemical Data of Organic Compounds*, 2nd Edition, J. B. Pedley, R. O. Naylor, and S. P. Kirby, Chapman and Hall, London, 1986.

(2,2,3,3-tetramethylbutane) of the C_8 isomers. For alkenes, substitution on the double bond is stabilizing. There is a range of nearly 7 kcal/mol for the C_6H_{12} isomers. The data for C_6 alkenes, for example show:



These relationships are a result of the stabilizing effect of branching and double-bond substitution and hold quite generally, except when branching or substitution results in van der Waals repulsions (see Section 2.3), which have a destabilizing effect.

3.1.2. Calculation of Enthalpy of Formation and Enthalpy of Reaction

In Chapter 1, we introduced various concepts of structure and the idea that the properties of molecules are derived from the combination of the properties of the atoms. One of the qualitative conclusions from these considerations is that the properties of CH_3 , CH_2 , CH , and C groups in hydrocarbons are expected to be similar from molecule to molecule, as long as they are not perturbed by a nearby functional group. Several methods for the calculation of thermodynamic data based on summation of group properties have been developed and are discussed in the next two sections.

3.1.2.1. Calculations of Enthalpy of Reaction Based on Summation of Bond Energies.

The computation of molecular energy by MO or DFT methods gives the *total binding energy* of a molecule. This is a very large number, since it includes all the electron-nuclei forces in the atoms, not just the additional attractive forces of the bonding electrons. The total energy can be converted to an energy representing all bonding between atoms by subtracting the energy of the individual atoms. This difference in energy is called the *energy of atomization*. This quantity still represents an energy that is far larger than the change involved in chemical reactions, which is of primary interest to chemists. The focus of chemical reactivity is on the bonds that are being formed and broken in the reaction. Useful relationships between structure and reactivity can be developed by focusing on *bond dissociation energies* (BDE). The most completely developed information pertains to *homolytic bond dissociation*,² which is the energy required to break a specific bond in a molecule with one electron going to each of the atoms. From the general bond energies in Part A of Table 3.2 we can discern several trends. One is that C–C bonds are considerably stronger than the other homonuclear bonds for the second-row elements (compare with O–O and N–N bonds). We can also note that the bonds in the dihalogens are relatively weak, with a somewhat irregular trend with respect to position in the periodic table: $F_2 < Cl_2 > Br_2 > I_2$. The bonds to hydrogen are also slightly irregular: $N < C < O < F$. For the hydrogen halides, there is a sharp drop going down the periodic table.

It is known that the immediate molecular environment significantly affects the bond energy, as is illustrated by the data in Part B of Table 3.2. For hydrocarbons the C–H bond dissociation energy depends on the degree of substitution and hybridization

². For a discussion of the measurement and application of bond dissociation energies, see S. J. Blanksby and G. B. Ellison, *Acc. Chem. Res.*, **36**, 255 (2003).

Table 3.2. Bond Energies (in kcal/mol)

A. Some Generalized Bond Energies ^a					
C—C	81	C—H	98	C=C	145
N—N	65	N—H	92	C≡C	198
O—O	34	O—H	105	N≡N	225
F—F	38	F—H	136	C=O	173
Cl—Cl	57	Cl—H	102	C—O	79
Br—Br	45	Br—H	87	C—N	66
I—I	36	I—H	71		

B. Some Specific Bond Dissociation Energies ^b					
CH ₃ —H	105.0	H ₃ C—CH ₃	90.2	H ₃ C—F	110.0
CH ₃ CH ₂ —H	100.5	H ₃ C ₂ —CH ₃	88.5	H ₃ C—Cl	83.7
(CH ₃) ₂ CH—H	98.1	(CH ₃) ₂ CH—CH ₃	88.2	H ₃ C—Br	70.3
(CH ₃) ₃ C—H	95.7	H ₅ C ₂ —C ₂ H ₅	86.8	H ₃ C—I	57.1
H ₂ C=CH—H	111.2	(CH ₃) ₂ CH—CH(CH ₃) ₂	84.1	CH ₃ CH ₂ —F	113.1
HC≡C—H	132.8	H ₂ C=CHCH ₂ —CH ₃	75.9	CH ₃ CH ₂ —Cl	84.2
H ₂ C=CHCH ₂ —H	88.2	H ₂ C=CH—CH=CH ₂	116.9	CH ₃ CH ₂ —Br	70.0
Ph—H	112.9	H ₂ C=CH ₂	174.1	CH ₃ CH ₂ —I	55.8
PhCH ₂ —H	88.5	HC≡CH	229.5	(CH ₃) ₂ CH—F	115.4
HC≡CHCH ₂ —H	88.9	Ph—CH ₃	102.0	(CH ₃) ₂ CH—Cl	84.6
H ₂ N—H	108.2	PhCH ₂ —CH ₃	76.4	(CH ₃) ₂ CH—Br	71.5
CH ₃ NH—H	101.6			(CH ₃) ₂ CH—I	56.1
CH ₃ O—H	104.2			H ₃ C—OH	92.0

a. From Table 1, G. J. Janz, *Thermodynamic Properties of Organic Compounds*, Academic Press, New York, 1967.

b. Y. R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, Boca Raton, FL, 2002

of the carbon atom. Primary, secondary, and tertiary sp^3 C—H, sp^2 C—H, and sp C—H bonds have characteristic values that are significantly different from one another. The variation in bond strengths is related to the stability of the resulting radicals. For C—H bonds, for example, the decrease in bond strength methane $> pri > sec > tert$ reflects the increasing stability of the more highly substituted carbon radicals. The extra strength of the C—H bond to sp^2 and sp carbons, as reflected by ethene, ethyne, and benzene, is due in part to the poor stability of ethenyl, ethynyl, and phenyl radicals. The relatively weak primary C—H bonds in propene and methylbenzene reflect conjugative stabilization of the resulting allyl and benzyl radicals (see Section 3.4.3).

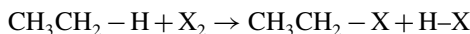
A direct approach to estimation of the ΔH for a reaction is to apply the fundamental thermodynamic relationship,

$$\Delta H = \Delta H_f^\circ \text{ reactants} - \Delta H_f^\circ \text{ products} \quad (3.3)$$

This equation is exact, but can be applied only if the thermodynamic data pertaining to the actual reaction conditions are available. Thermodynamic manipulations can be used to account for changes in temperature or pressure, but solvation energies are often uncertain (see Section 3.8). The relationship in Equation (3.3) can be approximated by

$$\Delta H = \text{BDE}_{\text{bonds formed}} - \text{BDE}_{\text{bonds broken}} \quad (3.4)$$

For example, data from Table 3.2 can be used to calculate the ΔH for reaction of each of the halogens with ethane. The strong trend in exothermicity of $F_2 > Cl_2 > Br_2 > I_2$ is evident:



X	Break		Form		
	$\text{CH}_3\text{CH}_2-\text{H}$	X_2	$\text{CH}_3\text{CH}_2-\text{X}$	$\text{H}-\text{X}$	ΔH
F	100.5	38	113.1	109	-83.6
Cl	100.5	57	84.2	102	-28.7
Br	100.5	45	70.0	87	-11.5
I	100.5	36	55.8	71	+9.7

While bonds of similar type, e.g., C–C, C–O, C–Cl, are of approximately the same strength, the precise value depends on both hybridization and the degree of substitution. For instance, as can be seen in Table 3.2, there is a range from 105.0 to 95.7 kcal/mol for the C–H bonds in methane, ethane, propane (C(2)–H), and isobutane (C(2)–H). The differences between C–H bonds for sp^3 , sp^2 , and sp carbon is even greater, as can be seen from the significantly different C–H BDE values for ethane, ethene, ethyne, and benzene. Similarly, C–C bonds between sp^2 carbons are considerably stronger than those between two sp^3 carbons, as is indicated by the C(2)–C(3) BDE of 116.9 kcal/mol for 1,3-butadiene. For estimation of reaction enthalpy using Equation (3.4), the most appropriate BDE must be chosen.

3.1.2.2. Relationships between Bond Energies and Electronegativity and Hardness. In his efforts to correlate important chemical properties, Pauling recognized that the difference in electronegativity between two bonded atoms contributes to bond strength. He proposed the empirical relationship

$$\text{BDE}_{\text{AB}} = 1/2(\text{BDE}_{\text{AA}} + \text{BDE}_{\text{BB}}) + 23(\Delta\chi)^2 \quad (3.5)$$

where $\Delta\chi$ is the difference in electronegativity of the two atoms. A related expression is

$$\text{BDE}_{\text{AB}} = (\text{BDE}_{\text{AA}} \times \text{BDE}_{\text{BB}})^{1/2} + 30(\Delta\chi)^2 \quad (3.6)$$

Both relationships propose that BDE is a function of the strength of the two homonuclear bonds and an increment for electronegativity differences.³ Although the quantitative reliability of the relationships in Equations (3.5) and (3.6) is limited, the equations do indicate that there is an increment to bond strength that is related to electronegativity differences. Subsequently, many investigators have probed the accuracy, scope, and theoretical foundation of these relationships and have suggested other formulations that improve the accuracy.⁴ A refinement of the empirical relationship that includes a term for polarizability gives the equation

$$\text{BDE}_{\text{AB}} = [\text{BDE}_{\text{AA}} \times \text{BDE}_{\text{BB}}]^{1/2} + |2.883(\Delta\chi)|^{[\alpha(\text{A})+\alpha(\text{B})]} \quad (3.7)$$

where α are polarizability parameters for each element.⁵ The polarizability parameters particularly improve the relationship for third-row atoms and other highly polarizable groups.

³ L. Pauling, *J. Am. Chem. Soc.*, **54**, 3570 (1932); L. Pauling, *The Nature of the Chemical Bond*, 3rd Edition, Cornell University Press, Ithaca, NY, 1960, Chap. 3.

⁴ R. R. Reddy, T. V. R. Rao, and R. Viswanath, *J. Am. Chem. Soc.*, **111**, 2914 (1989).

⁵ J. W. Ochterski, G. A. Petersson, and K. B. Wiberg, *J. Am. Chem. Soc.*, **117**, 11299 (1995).

The original Pauling equation was reexamined recently by Zavitsas and co-workers.⁶ The equation was shown to give quite good agreement with thermochemical data. Furthermore, it permitted assignment of electronegativity and *stabilization energy* to important radicals. The stabilization energy SE is assigned as

$$SE = 1/2(BDE_{[CH_3-CH_3]} - BDE_{[X-X]}) \quad (3.8)$$

Some values are given in Table 3.3. For future reference, note the order of radical stabilization: alkyl > alkenyl > alkynyl and allyl > benzyl > tertiary > secondary > primary. In Section 3.4.3, we discuss the structural basis of these relationships.

Another idea underlying the nature of bond formation is the concept of *electronegativity equalization*⁷ or *electronegativity equilibration*⁸ (see Section 1.1.4). This concept states that electron density flows from the less electronegative partner in a bond (making it more positive and therefore more electronegative) to the more electronegative atom (making it more negative and therefore less electronegative) until both atoms have the same effective electronegativity. At that point, there is no net attractive force on the electrons in the bond. This intuitively compelling idea has a theoretical foundation in DFT, which states that the chemical potential μ is uniform throughout a molecule. It is observed that the apparent bond strength for several series of compounds increases in the order $CH_3-X < pri-X < sec-X, tert-X$.⁹ The differences *increase* with the electronegativity of the substituent X. These electronegativity relationships lead to some qualitative trends. For alkyl groups with electronegative substituents, such as halogens, oxygen, or nitrogen, the trend is *tert* > *sec* > *pri* > CH_3 . On the other hand, for organometallics, alanes, and boranes, the order is reversed. Compounds that can readily interconvert can isomerize in response to these stability relationships.¹⁰

**Table 3.3. Group Electronegativity and Stabilization Energies (in kcal/mol)
Based on the Pauling Equation^a**

Group	χ	SE	Group	χ	SE
CH ₃	2.525	0.0	HO	3.500	
C ₂ H ₅	2.462	1.2	CH ₃ O	3.439	26.0
<i>i</i> -C ₃ H ₇	2.411	1.4	PhO	3.376	43.1
<i>t</i> -C ₄ H ₉	2.378	3.7	CH ₃ NH	3.018	13.5
CH ₂ =CHCH ₂	2.488	14.3	(CH ₃) ₃ Si	1.838	5.9
PhCH ₂	2.506	11.7	F	3.938	25.9
Ph		-13.1	Cl	3.174	15.9
CH ₂ =CH		-11.6			
HC≡C		-32.1			
CH ₃ C=O		7.9			

a. N. Matsunaga, D. W. Rogers, and A. A. Zavitsas, *J. Org. Chem.*, **68**, 3158 (2003).

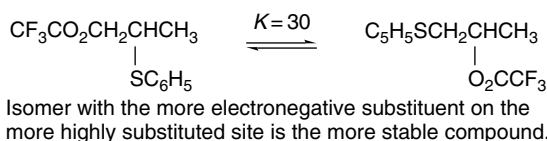
⁶ N. Matsunaga, D. W. Rogers, and A. A. Zavitsas, *J. Org. Chem.*, **68**, 3158 (2003).

⁷ S. G. Bratsch, *J. Chem. Educ.*, **61**, 588 (1984); R. T. Sanderson, *Polar Covalence*, Academic Press, New York, 1983.

⁸ D. W. Smith, *J. Chem. Educ.*, **67**, 559 (1990).

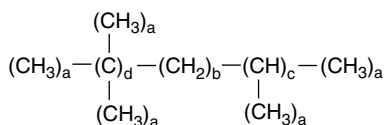
⁹ Y. R. Luo and S. W. Benson, *J. Phys. Chem.*, **92**, 5255 (1988); Y. R. Luo and S. W. Benson, *Acc. Chem. Res.*, **25**, 375 (1992); N. Laurencelle and P. D. Pacey, *J. Am. Chem. Soc.*, **115**, 625 (1993).

¹⁰ J. N. Harvey and H. G. Viehe, *J. Prakt. Chem. Chem. Zeitung*, **337**, 253 (1995).

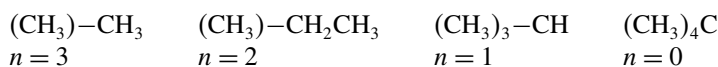


These treatments of bond energies illustrate that there are fundamental relationships between bond strengths and atomic properties such as electronegativity and polarizability. The crucial point is that bond strength *is increased by electronegativity differences in a given row of the periodic table* as a result of an increment that is due to electrostatic attraction.

3.1.2.3. Calculation of ΔH_f Using Transferable Group Equivalents. The idea that the properties of molecules are the sum of its component atoms and groups has led to the development of schemes by which thermodynamic properties can be calculated as the sum of contributions from all structural units.¹¹ The most highly developed is that of S. W. Benson and co-workers.¹² The molecule is divided into its component groups. For example, isooctane (which incidentally is the standard for 100 in octane ratings) consists of five C-(C)(H)₃ (a), one C-(C)₂(H)₂ (b), one C-(C)₃(H) (c), and one C-(C)₄ (d), as labeled on the structure.



The four groups designated above are sufficient to describe all alkanes. Finer distinctions can be made if these groups are subdivided further, depending on the number of hydrogens on the adjacent carbon. For example, a CH₃ group might be found in four different environments:



Modified increments are also assigned to carbons adjacent to double or triple bonds or benzene rings. The enthalpy of formation of a molecule can then be calculated as the sum of the contributions of the component groups. The main limitation of this method is that it does not explicitly consider long-range nonbonded interactions. The group equivalents refer to *strain-free molecules*. Further refinement can be incorporated by taking account of nonbonded interactions. For example, *gauche* interactions can be counted and applied as a correction to the sum of group equivalents.¹³

¹¹. For a discussion of the pioneering efforts in this field, see J. D. Cox and G. Pilcher, *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, New York, 1970, Chap. 7.

¹². N. Cohen and S. W. Benson, *Chem. Rev.*, **93**, 2419 (1993).

¹³. N. Cohen and S. W. Benson, *The Chemistry of Alkanes and Cycloalkanes*, S Patai and Z. Rappoport, eds., Wiley, 1992, Chap. 6; S. W. Benson and N. Cohen, in *Computational Thermodynamics*, K. K. Irikura and D. J. Frurip, eds., *ACS Symposium Series*, **677**, 20 (1996).

CHAPTER 3

Structural Effects on
Stability and Reactivity

5 C-(C)(H ₃) _a	-10.00	-50.00
1 C(C) ₂ (H ₂) _b	-5.00	-5.00
1 C(C) ₃ (H) _c	-2.40	-2.40
1 3C(C) ₄	-0.10	-0.10
3 <i>gauche</i> correction	-0.80	+2.40
Calculated value		-55.10

Group equivalent methods can be extended to functionalized compounds by assigning the enthalpy components of the substituent groups.¹⁴

Various other methods for making calculations based on bond dissociation energies more precise have been developed. A method developed by G. Leroy and co-workers is based on extensive thermochemical data, as well as energies calculated by MO methods.¹⁵ The heat of atomization of unstrained hydrocarbons is equated to the number of C–C and primary, secondary and tertiary C–H bonds. The heat of atomization is given by

$$\Delta H_{\text{atom}} = N_{\text{cc}}(E_{\text{cc}}) + N_{\text{pri}}(E_{\text{C-H}_{\text{pri}}}) + N_{\text{sec}}(E_{\text{C-H}_{\text{sec}}}) + N_{\text{tert}}(E_{\text{C-H}_{\text{tert}}}) \quad (3.9)$$

For stable compounds with known ΔH_{atom} the stabilization (or destabilization) is then the difference between ΔH_{atom} and the calculated sum of standard bond energies:

$$\text{SE} = \Delta H_{\text{atom}} - \Sigma \text{BE}_{\text{standard}} \quad (3.10)$$

Leroy and co-workers developed an extensive series of standard bond energy terms. Terms for specific substituent effects were also assigned, e.g., the $\Delta(\text{C}_d\text{--C})$ and $\Delta(\text{C--H})^{\text{O}}$ terms are adjustments for bonds between double bonds and having oxygen substituents, respectively. Comparison of the sum of the standard BE with the actual ΔH_{atom} gives the extra stabilization present in the compound. Calculations for butadiene stabilization (conjugation) and dimethoxymethane (anomeric effect) are given below.

Butadiene			Dimethoxymethane		
Bond energies:	$2E(\text{C}=\text{C})$	2(137.23)	Bond energies	$4E(\text{C--O})$	4(91.66)
	$4E(\text{C}_d\text{--H})_2$	4(100.30)		$2E(\text{C--H})_s$	2(97.53)
	$2E(\text{C}_d\text{--H})_1$	2(99.78)		$4\Delta(\text{C--H})_s^{\text{O}}$	4(-2.05)
	$E(\text{C--C})$	85.44		$6E(\text{C--H})_p^{\text{O}}$	6(95.87)
	$2\Delta(\text{C}_d^c\text{--C})$	2(3.88)			
	$\Sigma N_{\text{AB}} B_{\text{AB}} =$	968.42 kcal/mol ⁻¹		$\Sigma N_{\text{AB}} B_{\text{AB}} =$	1128.72 kcal/mol ⁻¹
ΔH_{atom}		971.5	ΔH_{atom}		1133.06
	SE	3.08 kcal/mol		SE	4.34 kcal/mol

The enthalpy change of a homolytic bond dissociation is expressed as the difference in stabilization of the products and reactants. A virtue of this approach is

¹⁴ J. B. Pedley, R. D. Naylor, and S. P. Kirby, *Thermochemical Data of Organic Compounds*, 2nd Edition, Chapman and Hall, London, 1986, Chap. 2.

¹⁵ G. Leroy, M. Sana, and C. Wilante, *J. Mol. Structure: Theochem.*, **234**, 303 (1991).

that it recognizes that there may be special stabilization, e.g., conjugation and anomeric effects, in the reactants as well as in the dissociated radicals.

$$\text{BDE} = \sum_{\text{R-Z}} \cdot \text{BE}_{\text{standard}} - \sum_{\text{R}\cdot} \text{BE}_{\text{standard}} - \sum_{\text{Z}\cdot} \text{BE} + \text{SE}_{\text{R-Z}} - \text{SE}_{\text{R}\cdot} - \text{SE}_{\text{Z}\cdot} \quad (3.11)$$

Table 3.4 gives some representative results.

According to this analysis, the weakening of the C–H bonds in isobutane and toluene is largely due to the stabilization of the resulting radicals. However, even though trichloromethyl radicals are quite stable, there is also considerable stabilization in the starting material chloroform, and the C–H bond in chloroform is not weakened as much as that in isobutane. More is said about separating structural effects in reactant and intermediate radicals in Topic 11.1.

The calculation of ΔH_f° is now usually done by computational chemistry, but the success of the group equivalent approaches makes an important point. The properties of groups are very similar from molecule to molecule, similar enough to make additivity schemes workable. However, *specific interactions*, e.g., nonbonded interactions, that depend on the detailed structure of the molecule are not accounted for. Whenever interactions that are not accounted for by the group equivalents exist, there will be a discrepancy between the calculated and actual properties of the molecule. Analyses such as that of Leroy can provide valuable insights and concepts. In particular, they provide a means for recognizing stabilization effects present in reactants, as demonstrated by the calculations for 1,3-butadiene and dimethoxymethane.

3.1.2.4. Calculation of Enthalpy of Formation by Molecular Mechanics. Molecular mechanics (MM) is a systematic approach to the calculation of molecular energy based on the summation of bond properties and nonbonding (e.g., van der Waals) interactions (review Section 2.4). MM provides a means for analyzing the energy differences between molecules and among various geometries of a particular molecule.¹⁶ Several systems of parameters and equations for carrying out the calculations have been developed. The method most frequently used in organic chemistry is the one developed by N. L. Allinger and co-workers.¹⁷ In the most recent version of MM calculations

**Table 3.4. Calculation of the C–X Bond Dissociation Energies
(in kcal/mol; 298.15 K)**

R–X	$\Delta \sum N_{\text{AB}} E_{\text{AB}}$	$\text{SE}_0(\text{R} - \text{X})$	$\text{SE}_0(\text{R}\cdot)$	$\text{BDE}(\text{R} - \text{X})$
Et–H	99.8	0	0	100.3
t-Bu–H	96.8	0.8	3.7	93.9
Et–Cl	83.3	0	–0.5	83.8
t-Bu–Cl	85.6	0	3.7	81.9
C ₆ H ₅ CH ₂ –H	99.8	–1.0	11.6	87.1
(t-Bu) ₂ CH–H	98.2	–6.0	–5.9	98.2
Cl ₃ C–H	93.9	–16.3	–18.0	95.7

¹⁶ F. H. Westheimer, in *Steric Effects in Organic Chemistry*, M. S. Newman, ed., Wiley, New York, 1956, Chap. 12; J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19**, 531 (1968); D. B. Boyd and K. P. Lipkowitz, *J. Chem. Educ.*, **59**, 269 (1982); P. J. Cox, *J. Chem. Ed.*, **59**, 275 (1982); N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1 (1976); E. Osawa and H. Musso, *Top. Stereochem.*, **13**, 117 (1982); U. Burkett and N. L. Allinger, *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington, DC, 1982.

¹⁷ N. L. Allinger, Y. H. Yuh, and J. -H. Li, *J. Am. Chem. Soc.*, **111**, 8551 (1989).

for organic molecules, known as MM4,¹⁸ the computations involve iterations to locate an energy minimum. Precautions must be taken to establish that a true (“global”) minimum, as opposed to a local minimum energy, is found. This can be accomplished by using a number of different initial geometries and comparing the structures of the minima that are located. As with the group equivalent approach, MM calculations of ΔH_f° are grounded in experimental measurements of a limited number of molecules that were used to optimize the parameters. The original parameters pertained to hydrocarbons, but as the method has developed, the parameters have been extended to many functional groups. MM calculations specifically take molecular geometry into account, including nonbonded and dipolar interactions. Van der Waals interactions are described in terms of energy functions and parameters that describe the interaction of the approaching atoms. Polar interactions are modeled as electrostatic interactions.

Heats of formation are calculated as a sum of the bond energies and other stabilizing and destabilizing (e.g., strain) increments for the structure. MM4 calculations include terms for contributions of higher-energy conformations.¹⁹ For a set of hydrocarbons ranging from methane and ethane to adamantane and bicyclo[2.2.2]octane, the heats of formation are calculated with a standard deviation of 0.353 kcal/mol. The MM4 system has also been applied to alkenes,²⁰ aldehydes,²¹ and ketones.²²

3.1.2.5. Thermodynamic Data from MO and DFT Computations. MO and DFT calculations provide another approach to obtaining thermodynamic data. The accuracy with which the various computational methods reproduce molecular energies varies. Of the semiempirical methods only MINDO,²³ MNDO²⁴, AM1,²⁵ and PM3²⁶ provide reliable estimates of energies and the range of applicability is open to some discussion.²⁷ Among the ab initio methods the level of accuracy generally increases with larger basis sets and treatment of correlation effects. G1, G2, and G3 computations can achieve a level of accuracy that permits comparison of energy data among related molecules. DFT calculations have also been applied to various compounds.²⁸ Users of computational thermochemical data must critically assess the reliability of the method being applied in the *particular case* under study.

A large series of compounds, including hydrocarbon derivatives, was studied at the G2 and G2(MP2,SVP) levels and compared with results from the B3LYP method.²⁹ Another group carried out a similar comparison on a smaller set of molecules.³⁰

¹⁸ N. L. Allinger, K. Chen, and J. -H. Lii, *J. Comput. Chem.*, **17**, 642 (1996).

¹⁹ N. L. Allinger, L. R. Schmitz, I. Motoc, C. Bender, and J. Labanowski, *J. Phys. Org. Chem.*, **3**, 732 (1990); N. L. Allinger, L. R. Schmitz, I. Motoc, C. Bender, and J. Labanowski, *J. Am. Chem. Soc.*, **114**, 2880 (1992).

²⁰ N. Nevins, K. Chen, and N. L. Allinger, *J. Comput. Chem.*, **17**, 695 (1996).

²¹ C. H. Langley, J. H. Lii, and N. L. Allinger, *J. Comput. Chem.*, **22**, 1396 (2001).

²² C. H. Langley, J. H. Lii, and N. L. Allinger, *J. Comput. Chem.*, **22**, 1426, 1451, 1476 (2001).

²³ R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, **97**, 1294 (1975).

²⁴ M. J. S. Dewar and G. P. Ford, *J. Am. Chem. Soc.*, **101**, 5558 (1979).

²⁵ M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).

²⁶ J. J. P. Stewart, *J. Comput. Chem.*, **10**, 221 (1989).

²⁷ J. A. Pople, *J. Am. Chem. Soc.*, **97**, 5307 (1975); T. A. Halgren, D. A. Kleier, J. H. Hall, Jr., L. D. Brown, and W. L. Lipscomb, *J. Am. Chem. Soc.*, **100**, 6595 (1978); M. J. S. Dewar and D. M. Storch, *J. Am. Chem. Soc.*, **107**, 3898 (1985).

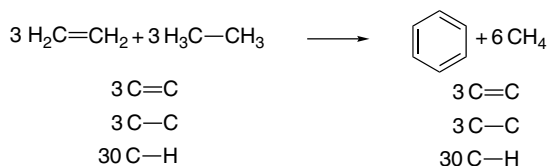
²⁸ K. Raghavachari, B. B. Stefanov, and L. A. Curtiss, *Molec. Phys.*, **91**, 555 (1997); B. S. Jursic, *Theochem*, **391**, 75 (1997); B. S. Jursic, *Theochem*, **417**, 99 (1997); J. Andzelm, J. Baker, A. Scheiner, and M. Wrinn, *Int. J. Quantum Chem.*, **56**, 733 (1995).

²⁹ L. A. Curtiss, K. Raghavachari, P. C. Redfern, and J. A. Pople, *J. Chem. Phys.*, **106**, 1063 (1997).

³⁰ J.-W. Pan, D. W. Rogers, and F. J. McLafferty, *Theochem.*, **468**, 59 (1999).

Table 3.5 includes the B3LYP/6-311 + G(3df,2p) results for some small hydrocarbons. MO and DFT calculations pertain to molecules at 0 K without any molecular motion. In order to make comparisons with thermodynamic data at 298 K, corrections for both zero-point energy (ZPE) and the difference in thermal energy must be made. The corrections are normally incorporated into calculations intended for thermochemical comparisons. The corrections are based on calculation of the vibrations and rotations that contribute to ZPE and thermal energy. Table 3.5 gives a comparison of some calculated ΔH_f with experimental values for some simple hydrocarbons. The absolute errors are small for methods such as G2, CBS-Q, and CBS-QB. There are some indications that B3LYP calculations tend to underestimate the stability of hydrocarbons as the size of the molecule increases. For example, using the 6-311 + G(3df,2p) basis set, the error increased systematically from propane (−1.5 kcal/mol) to hexane (−9.3) and octane (−14.0).³¹ Similarly, the effect of successively adding methyl groups to ethane resulted in an error of 21.1 kcal/mol for 2,2,3,3-tetramethylbutane.³²

MO methods can also be used to calculate *heats of reaction* by comparing the heats of formation of reactants and products. The *total energy* calculated for even a small hydrocarbon, relative to the separate nuclei and electrons, is enormous (typically 50,000 and 100,000 kcal/mol for C₂ and C₄ compounds, respectively) relative to the energy of reaction. Sometimes the energy is tabulated as the *energy of atomization*, corresponding to the difference in total energy of the molecule and that of the separate atom, which is the energy required to break all the bonds. These values, too, are very large in comparison with the heat of reaction. The energy differences that are of principal chemical interest, such as ΔH for a reaction, are likely to be in the range of 0–30 kcal/mol. A very small error relative to the total energy in an MO calculation becomes a very large error in a calculated ΔH . Fortunately, the absolute errors for compounds of similar structure are likely to be comparable and tend to cancel in calculation of the *energy differences* between related molecules. Calculation of heats of formation and heats of reaction is frequently done on the basis of *isodesmic reactions*,³³ in order to provide for maximum cancellation of errors in total binding energies. An isodesmic reaction is defined as a process in which the number of formal bonds of each type is kept constant; that is, there are the same number of C–H, C=C, C=O, etc., bonds on each side of the equation.³⁴ For example, an isodesmic reaction to evaluate the stability of benzene would be:



The comparison can be further refined by use of *homodesmotic reactions* in which there is matching not only of bond types, but also of hybridization. Thus in the reaction

³¹. L. A. Curtiss, K. Raghavachari, P. C. Redfern, and J. A. Pople, *J. Chem. Phys.*, **112**, 7374 (2000).

³². C. E. Check and T. M. Gilbert, *J. Org. Chem.*, **70**, 9828 (2005).

³³. W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4796 (1970).

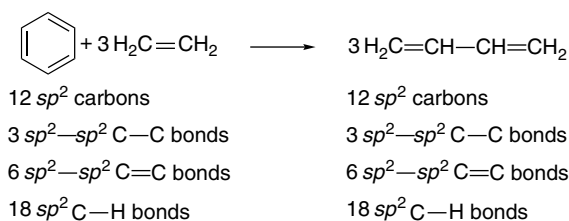
³⁴. D. A. Ponomarev and V. V. Takhistov, *J. Chem. Ed.*, **74**, 201 (1997).

Table 3.5. Comparison of Differences between Calculated and Experimental ΔH_f in kcal/mol for some Hydrocarbons.^a

Hydrocarbon	MNDO ^a	AMI ^b	PM3 ^c	HF/3-21G ^a	HF/6-31G ^a	G2 ^d	CBS-Q ^e	CBS-QB3 ^f	MP4/QCI ^g	B3LYP/6-311+G(3d,f,2p) ^h
Methane	5.9	9.0	4.9	-0.9	-0.5	0.7	-0.2	-0.4	-0.6	-1.6
Ethane	0.3	2.6	2.1	0.2	0.9	-0.2	-0.6	-0.6	-0.7	0.0
Butane	0.7	-0.7		-0.8	-0.8	0.6				-0.8
Pentane	0.7	-2.8		-0.5	-0.5					
Cyclopropane	-1.5	5.1	3.5		-2.4					-0.6
Cyclobutane	-18.7	0.2	-10.6				-1.7			1.2
Cyclopentane	-12.0	-10.5	-5.6		-6.1		-3.4	-0.1		4.5
Cyclohexane	-5.3	-9.0	-1.5		-9.1	3.9		-0.1		
Ethene	3.1	4.0	4.2	-1.6	-2.4	0.3	-1.0	0.0	0.1	-0.5
Allene	-1.6	0.6	1.5	-2.5	-6.8	0.0 ⁱ	1.3	0.0		-2.4
1,3-Butadiene	2.7	3.6	5.0	-4.7	-2.9	0.5 ^j		0.7		-1.5 ^d
Benzene		1.5	2.2	3.6		4.0 ^k	1.5	-0.2		-4.0 ^d
Bicyclo[2.2.1]heptane	2.1	-2.0	-1.3		8.8					
Bicyclo[2.2.2]octane	-2.2	-11.9	-3.7		10.7					

^a M. J. S. Dewar, E. G. Zoebisch, E.F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).^b M. J. S. Dewar and D. M. Storch, *J. Am. Chem. Soc.*, **107**, 3898 (1985).^c J. J. P. Stewart, *J. Comput. Chem.*, **10**, 221 (1989).^d J. A. Pople, M. Head-Gordon, D. J. Fox, K. Raghavachari, and L. A. Curtiss, *J. Chem. Phys.*, **90**, 5622 (1989); L. A. Curtiss, K. Raghavachari, G. W. Trucks, and J. A. Pople, *J. Phys. Chem.*, **94**, 7221 (1991); L. A. Curtiss, K. Raghavachari, P. C. Redfern, and J. Pople, *J. Chem. Phys.*, **106**, 1063 (1997).^e L. A. Curtiss, K. Raghavachari, P. C. Redfern, and B. B. Stefanov, *J. Chem. Phys.*, **108**, 692 (1998).^f M. Saeys, M. -F. Reynders, G. B. Marin, V. Van Speybroeck, and M. Waroquier, *J. Phys. Chem. A*, **107**, 9147 (2003).^g M. Sana and M. T. Nguyen, *Chem. Phys. Lett.*, **196**, 390 (1992).^h J. -W. Pan, D. W. Rogers, and F. J. McAfferty, *Theochem*, **468**, 59 (1999).ⁱ D. W. Rogers and F. J. McAfferty, *J. Phys. Chem.*, **99**, 1375 (1993).^j M. N. Glukhovtsev and S. Laiter, *Theor. Chim. Acta*, **92**, 327 (1995).^k A. Nicolaides and L. Radom, *J. Phys. Chem.*, **98**, 3092 (1994).

below, the number of sp^3 , sp^2 , and sp C—H bonds and the hybridization types of the C—C bonds are balanced.³⁵



Further refinements are possible. For example, in evaluating cyclic compounds, use of matching ring sizes can be specified so as to cancel errors resulting from ring strain.³⁶ Although the reaction may not correspond to any real chemical process, the calculation can test the reliability of the computation methods because of the additivity of ΔH_f° data.

The accuracy of the computational ΔH can be judged by comparison with ΔH obtained by summation of tabulated ΔH_f° for reactants and products. Table 3.6 compares some ΔH_f° values calculated at the G2 level of theory from atomization energies and isodesmic reactions. For molecules of this size, the use of isodesmic reactions can usually achieve ΔH_f° data within 0.5 kcal/mol.³⁷ A study of a series of hydrocarbons, including somewhat larger molecules, comparing G2 and G3 calculations is also available.³⁸

For larger molecules that are outside the range of ab initio calculations, the semiempirical methods can be used. For example, the AM1 and PM3 methods have been used for a series of polycyclic aromatic hydrocarbons. Some results are shown in Table 3.7. The average errors were 9.1 kcal/mol for AM1 and 5.9 for PM3. Both methods can be internally calibrated by least-squares correlations, which improve the average error to 1.3 kcal/mol for AM1 and 2.1 for PM3.

Table 3.6. Comparison of Differences from Experimental ΔH_f° in kcal/mol for G2 Calculations Using Atomization Energy versus Isodesmic Reactions^a

	ΔH_f° (exp)	G2 (atomization)	G2 (isodesmic)
Propane	−25.0	0.4	0.1
Cyclopropane	66.0	−2.9	−1.6
Butane	−30.0	0.4	0.2
Cyclobutane	37.4	−2.9	−1.5
Bicyclo[1.1.0]butane	51.9	−3.0	−1.5
Cyclopentane	−18.3	−1.1	−0.4
Benzene	19.7	−3.9	−0.8

a. K. Raghavachari, B. Stefanov, and L. A. Curtiss, *J. Chem. Phys.*, **106**, 6764 (1997).

³⁵. P. George, M. Trachtman, C. W. Bock, and A. M. Brett, *Tetrahedron*, **32**, 317 (1976).

³⁶. P. v. R. Schleyer, P. K. Freeman, H. Jiao, and B. Goldfuss, *Angew. Chem. Int. Ed. Engl.*, **34**, 337 (1995); M. K. Cyranski, P. v. R. Schleyer, T. M. Krygowski, H. Jiao, and G. Hohlneicher, *Tetrahedron*, **59**, 1657 (2003).

³⁷. K. Raghavachari, B. B. Stefanov, and L. A. Curtiss, *J. Chem. Phys.*, **106**, 6764 (2000).

³⁸. R. Notario, O. Castano, J. -L. M. Abboud, R. Gomperts, L. M. Frutos, and R. Palmeiro, *J. Org. Chem.*, **64**, 9011 (1999); R. Notario, O. Castano, R. Gomperts, L. M. Frutos, and R. Palmeiro, *J. Org. Chem.*, **65**, 4298 (2000).

Table 3.7. Comparison of Experimental ΔH_f° (kcal/mol) and Semiempirical Values for Polycyclic Aromatic Hydrocarbons

Molecule ^a	Experimental ΔH_f°	AM1 ^b	PM3 ^c
Benzene	20.0	22.0	23.5
Naphthalene	36.0	40.6	40.7
Phenanthrene	49.7	57.4	55.0
Anthracene	55.2	62.5	61.7
Pyrene	54.0	67.4	64.1
Triphenylene	66.5	75.5	68.3
Chrysene	66.0	76.2	70.9
Benz[a]anthracene	70.3	78.3	74.5
Benzo[c]phenanthrene	69.6	81.2	77.6
Perylene	78.4	89.3	82.0
Tetracene	72.3	86.9	84.3

a. For structures of the polycyclic aromatic hydrocarbons, see Scheme 8.2, p. 746.








b. W. C. Herndon, P. C. Nowak, D. A. Connor, and P. Lin, *J. Am. Chem. Soc.*, **114**, 41 (1992).

c. D. M. Camaioni, S. T. Autrey, T. B. Salinas, and J. A. Franz, *J. Am. Chem. Soc.*, **118**, 2013 (1996)

Any set of computed energies can be used for calculation of reaction enthalpies by comparing the energy of reactants and products. Table 3.8 gives some data for hydrogenation, hydrogenolysis, and isomerization reactions at several levels of theory, including data for small ring compounds, which represent a particularly challenging test of the accuracy of the computational methods.

The relative merits of various computational methods have been discussed in the literature.³⁹ In general, the ab initio types of calculations are more reliable but

Table 3.8. Comparison of Calculated and Observed ΔH for Some Reactions^a

Reaction	HF/6-31G*	MP2/6-311*	B3LYP/6-31G*	Observed
$\text{CH}_2=\text{CH}_2 + \text{H}_2 \rightarrow \text{C}_2\text{H}_6$	-36.0	-32.2	-31.7	-30.8
$\text{CH}_2=\text{CHCH}=\text{CH}_2 + 2\text{H}_2 \rightarrow \text{C}_4\text{H}_{10}$	-62.5	-55.6	-52.4	-53.3
 + 3H ₂ → C ₆ H ₁₂	-53.8	-41.1	-38.1	-44.0
$\text{C}_2\text{H}_6 + \text{H}_2 \rightarrow 2\text{CH}_4$	-18.8	-10.4	-16.5	-15.5
 + H ₂ → C ₃ H ₈	-41.8	-35.6	-38.6	-35.9
 → CH ₂ =CHCH ₃	-8.9	-6.2	-10.5	-8.5
 + H ₂ → C ₄ H ₁₀	-40.3	-34.1	-37.3	-35.9
 + H ₂ → 	-53.2	-44.0	-47.0	-44.4
 → CH ₂ =CHCH=CH ₂	-20.9	-22.4	-31.9	-26.2

a. In kcal/mol; K. B. Wiberg and J. W. Ochterski, *J. Comput. Chem.*, **18**, 108 (1997).

³⁹ J. A. Pople, *J. Am. Chem. Soc.*, **97**, 5306 (1975); W. J. Hehre, *J. Am. Chem. Soc.*, **97**, 5308 (1975); T. A. Halgren, D. A. Kleier, J. H. Hall, Jr., L. D. Brown, and W. N. Lipscomb, *J. Am. Chem. Soc.*, **100**, 6595 (1978); M. J. S. Dewar and G. P. Ford, *J. Am. Chem. Soc.*, **101**, 5558 (1979); W. J. Hehre, *Acc. Chem. Res.*, **9**, 399 (1976); M. J. S. Dewar, E.G. Zoebisch, E. F. Healy, and J. J. P. Stewart,

the semiempirical calculations are much faster in terms of computer time. The time requirement for an ab initio calculation increases rapidly as the number of atoms in the molecule increases. The C₈ hydrocarbons represent the current practical limit for high-level ab initio computations. DFT computations are faster than ab initio computations and the amount of computer time required does not increase as rapidly with molecular size. The choice of basis set orbitals influences the outcome, and often several basis sets are checked to determine which are adequate. A choice of computational method is normally made on the basis of evidence that the method is suitable for the problem at hand and the availability of appropriate computer programs and machine time. Results should be subjected to critical evaluation by comparison with experimental data or checked by representative calculations using higher-level methods.

3.1.2.6. Limitations on Enthalpy Data for Predicting Reactivity. Whether ΔH for a projected reaction is based on tabulated thermochemical data, bond energy, equivalent group additivity, or on MO or DFT computations, fundamental issues that prevent a final conclusion about a reaction's feasibility remain. In the first place, most reactions of interest occur in solution, and the enthalpy, entropy, and free energy associated with any reaction depend strongly on the solvent medium. There is only a limited amount of tabulated thermochemical data that are directly suitable for the treatment of reactions in organic solvents.⁴⁰ MO and DFT calculations usually refer to the isolated (gas phase) molecule. Estimates of solvation effects on reactants, products, intermediates, and transition states must be made in order to apply either experimental or computational thermochemical data to reactions occurring in solution. There may be substantial differences between solvation energies of reactants, transition states, intermediates, and products. If so, these solvation differences become a major factor in determining reactivity.

An even more fundamental limitation is that ΔH data give no information about the *rate of a chemical reaction*. It is the energy of the transition state relative to the reactants that determines the reaction rate. To be in a position to make judgments on reactivity, we have to see how structure is related to *reactivity*. To do this, we need information about the energy of transition states and intermediates, but because transition states are transitory, we have no physical means of determining their structure. We can, however, determine their energy relative to reactants on the basis of reaction kinetics. We address this topic in the next sections by first examining the principles of chemical kinetics. We can also obtain information about transition states and intermediates by studying the effect of substituents on the rate of reaction. In Section 3.4, we look at how key intermediates such as carbocations, carbanions, and radicals respond to substituents.

Theoretical descriptions of molecules have been applied to the structure of transition states and unobservable intermediates. By applying MO or DFT methods, structures can be calculated for successive geometries that gradually transform the reactants into products. Exploration of a range of potential geometries and calculation of the energy of the resulting ensembles can, in principle, locate and describe

J. Am. Chem. Soc., **107**, 3902 (1985); J. N. Levine, *Quantum Chemistry*, 3rd Edition, Allyn and Bacon, 1983, pp. 507–512; W. Hehre, L. Radom, P. v. R. Schleyer, and J. A. Pople, *Ab Initio Molecular Orbital Calculations*, John Wiley & Sons, 1986, Chap. 6; B. H. Besler, K. M. Merz, Jr., and P. Kollman, *J. Comput. Chem.*, **11**, 431 (1990); M. Sana and M. T. Nguyen, *Chem. Phys. Lett.*, **196**, 390 (1992).

⁴⁰. Guthrie has explored the use of a group equivalent scheme to compute ΔG_f° for aqueous solutions. J. P. Guthrie, *Can. J. Chem.*, **70**, 1042 (1992).

the minimum energy pathway. To the extent that the calculations accurately reflect the molecular reality, this provides a structural description of the reaction path and transition state. Thus we can refer to the *transition structure*, that is, the structural description of the reacting ensemble at the transition state.⁴¹ We use the abbreviation TS to refer to transition structures. We use the term *transition state* in the context of energetic analysis where there is no explicit consideration of the structure. In Section 3.7 we focus attention on another aspect of reactivity—the use of catalysts to accelerate reaction.

3.2. Chemical Kinetics

3.2.1. Fundamental Principles of Chemical Kinetics

Thermodynamic data give us a means of quantitatively expressing *stability*. Now we need to explore the relationship between *structure* and *reactivity*. The quantitative description of reactivity is called *chemical kinetics*. A fundamental thermodynamic equation relates the equilibrium constant for a reaction to the free-energy change associated with the reaction:

$$\Delta G = -RT \ln K \quad (3.12)$$

The free energy contains both enthalpy and entropy terms:

$$\Delta G = \Delta H - T\Delta S \quad (3.13)$$

Thus we see that thermodynamic stability, as measured by free energy, places a limit on the *extent of a chemical reaction*. However, it does not directly determine the rate of the reaction.

The nature of the *rate constants* k_r for individual steps in a chemical reaction can be discussed in terms of *transition state theory*, which is a general approach for analyzing the energetic and entropic components of a reaction process. In transition state theory, a reaction is assumed to involve the attainment of an *activated complex* that goes on to product at an extremely rapid rate. The rate of decomposition of the activated complex has been calculated from the assumptions of the theory to be about $6\text{--}10^{12} \text{ s}^{-1}$ at room temperature. The observed rate constant k_r is given by the expression⁴²

$$k_r = \frac{\kappa k_B T}{h} (e^{-\Delta H^\ddagger/RT}) (e^{\Delta S^\ddagger/R}) \quad (3.14)$$

⁴¹. Although the terms transition state and transition structure are often used interchangeably, if the transition state is taken as defined by transition state theory, it may differ in structure from the maximum energy obtained by computation; K. N. Houk, Y. Li, and J. D. Evans, *Angew. Chem. Int. Ed. Engl.*, **31**, 682 (1992).

⁴². For a more complete development of these relationships, see M. Boudart, *Kinetics of Chemical Processes*, Prentice-Hall, Englewood Cliffs, NJ, 1968, pp. 35–46; or I. Amdur and G. G. Hammes, *Chemical Kinetics: Principles and Selected Topics*, McGraw-Hill, New York, 1966, pp. 43–58; J. W. Moore and R. G. Pearson, *Kinetics and Mechanism*, Wiley, New York, 1981, pp. 159–169; M. M. Kreevoy and D. G. Truhlar, in C. F. Bernasconi, *Investigation of Rates and Mechanisms of Reaction: Techniques of Organic Chemistry*, 4th Edition, Vol. VI, Part 1, Interscience, New York, 1986.

in which κ is the transmission coefficient, which is usually taken to be 1, k_B is Boltzmann's constant, h is Planck's constant, R is the gas constant, and T is the absolute temperature. If the activated complex is considered to be in equilibrium with its component molecules, the attainment of the transition state (TS) can be treated as being analogous to a bimolecular reaction:

$$K^\ddagger = \frac{[TS]}{[A][B]} \quad (3.15)$$

The position of this equilibrium is related to the free energy required for attainment of the transition state. The symbol (‡) is used to specify that it is a transition state or "activated complex" that is under discussion:

$$\Delta G^\ddagger = -RT \ln K^\ddagger \quad (3.16)$$

The free energy ΔG^\ddagger is called as the *free energy of activation*. The rate of a reaction step is then given by

$$\text{Rate} = \frac{\kappa k_B T}{h} [TS] \quad (3.17)$$

$$\text{Rate} = \frac{\kappa k_B T}{h} e^{-\Delta G^\ddagger/RT} [A][B] \quad (3.18)$$

Comparison with the form of the expression for the rate of any single reaction step reveals that the magnitude of ΔG^\ddagger is the factor that determines the magnitude of k_r at any given temperature:

$$\text{Rate} = k_r [A][B] \quad (3.19)$$

The temperature dependence of reaction rates permits evaluation of the enthalpy and entropy components of the free energy of activation. The terms in Equation (3.14) can be rearranged to examine the temperature dependence:

$$k_r = \frac{\kappa k_B T}{h} \left(e^{-\Delta H^\ddagger/RT} \right) \left(e^{\Delta S^\ddagger/R} \right) \quad (3.20)$$

The term $(\kappa k_B T/h) e^{\Delta S^\ddagger/R}$ varies only slightly with T compared to $e^{-\Delta H^\ddagger/RT}$ because of the exponential nature of the latter. To a good approximation, then:

$$\frac{k_r}{T} = C e^{-\Delta H^\ddagger/RT} \quad (3.21)$$

$$\ln \frac{k_r}{T} = \frac{-\Delta H^\ddagger}{RT} + C' \quad (3.22)$$

A plot of $\ln(k_r/T)$ versus $1/T$ is a straight line, and its slope is $-\Delta H^\ddagger/R$. After ΔH^\ddagger is determined in this manner, ΔS^\ddagger is available from the relationship

$$\Delta S^\ddagger = \frac{\Delta H^\ddagger}{T} + R \ln \frac{h k_r}{\kappa k_B T} \quad (3.23)$$

which can be obtained by rearranging Equation (3.14).

The temperature dependence of reactions is frequently expressed in terms of the Arrhenius equation:

$$k_r = Ae^{-E_a/RT} \quad \text{or} \quad \ln k_r = -E_a/RT + \ln A \quad (3.24)$$

The E_a can be determined experimentally by measuring the reaction rate at several temperatures over as wide a range as practical. A plot of $\ln k_r$ against $1/T$ then gives a line of slope equal to $-E_a/R$. The value of E_a incorporates the ΔH term and the value of A reflects the entropy term. At constant pressure, E_a and ΔH are related by the expression

$$\Delta H^\ddagger = E_a - RT \quad (3.25)$$

and ΔS^\ddagger is related to A by

$$\Delta S^\ddagger = R[\ln(h/k_B T) + \ln A - 1] \quad (3.26)$$

The magnitude of ΔH^\ddagger and ΔS^\ddagger reflect transition state structure. Atomic positions in the transition state do not correspond to their positions in the ground state. In particular, the reacting bonds are partially formed or partially broken. The energy required for bond reorganization is reflected in the higher energy content of the activated complex and corresponds to the enthalpy of activation ΔH^\ddagger . The entropy of activation, ΔS^\ddagger , is a measure of the degree of organization resulting from the formation of the activated complex. If translational, vibrational, or rotational degrees of freedom are lost in going to the transition state, there is a decrease in the total entropy of the system. Conversely, an increase of translational, vibrational, or rotational degrees of freedom results in a positive entropy of activation. For reactions in solution, the organization of solvent contributes to the entropy of activation.

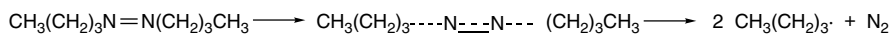
Wide variation in enthalpy and entropy of activation for different reaction systems is possible, as illustrated by the following two reactions.



$$\Delta H^\ddagger = 15.5 \text{ kcal/mol}$$

$$\Delta S^\ddagger = -34 \text{ eu}$$

Ref. 43



$$\Delta H^\ddagger = 52 \text{ kcal/mol}$$

$$\Delta S^\ddagger = +19 \text{ eu}$$

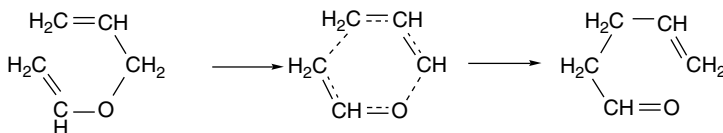
Ref. 44

The relatively low ΔH^\ddagger term for the dimerization of cyclopentadiene is characteristic of concerted reactions (see Chapter 10), in which bond making accompanies

⁴³. A. Wassermann, *Monatsch. Chem.*, **83**, 543 (1952).

⁴⁴. A. U. Blackham and N. L. Eatough, *J. Am. Chem. Soc.*, **84**, 2922 (1962).

bond breaking. It differs markedly from ΔH^\ddagger for the thermal decomposition of 1,1'-azobutane, in which the rate-determining step is a homolytic cleavage of a C–N bond, with little new bond making to compensate for the energy cost of the bond breaking. The entropy of activation, on the other hand, is more favorable in the 1,1'-azobutane decomposition, since a translational degree of freedom is being gained in the TS as the molecular fragments separate. The dimerization of cyclopentadiene is accompanied by a very negative entropy of activation because of the loss of translational and rotational degrees of freedom in formation of the highly ordered cyclic TS. The two reacting molecules must attain a specific orientation to permit the bonding interactions that occur as the TS is approached. Unimolecular reactions that take place by way of cyclic transition states also typically have negative entropies of activation because of the loss of rotational degrees of freedom associated with the highly ordered TS. For example, thermal isomerization of vinyl allyl ether to 4-pentenal has $\Delta S^\ddagger = -8 \text{ cal/mol-deg}^{-1}$.⁴⁵



It is important to remember that the enthalpy and entropy of activation reflect the response of the *reacting system as a whole* to formation of the activated complex. As a result, the interpretation of these parameters is more complicated for reactions taking place in solution than for gas phase reactions. This is particularly true for processes involving formation or destruction of charged species. The solvolysis of *t*-butyl chloride in 80% aqueous ethanol, for example, has as its rate-determining step unimolecular ionization of the carbon-chlorine bond to form chloride and *t*-butyl cations. One might think that this ionization would lead to a positive entropy of activation, since two independent particles are being generated. In fact, the entropy of activation is $-6.6 \text{ cal/mol-deg}^{-1}$. Owing to its polar character, the TS requires a greater ordering of solvent molecules than the nonpolar reactant.⁴⁶ Reactions that generate charged species usually exhibit negative entropies of activation in solution. The reverse is true for reactions in which charged reactants lead to a neutral transition state.

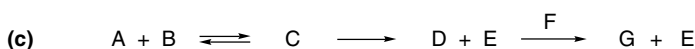
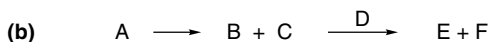
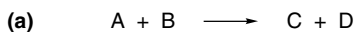
3.2.2. Representation of Potential Energy Changes in Reactions

3.2.2.1. Reaction Energy Profiles. It is often useful to describe reactions in terms of an energy profile that traces the potential energy of the reacting ensemble of molecules as they proceed from reactants to products, such as shown in Figure 3.1 (page 254). Thermodynamic stability establishes the relative energy of the reactants and the products, but does not provide any information about the intervening stages of the process. It is these intervening stages that determine how fast (or slow) a reaction will be. If a large ΔG^\ddagger is required, the reaction will be slow. Reactions often proceed through a sequence of steps involving formation of a series of intermediates that eventually lead to the products. Interpretation of the kinetic characteristics of a reaction can provide information about the intervening steps by providing information about *intermediates*

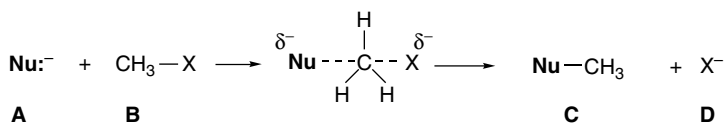
⁴⁵ F. W. Schuler and G. W. Murphy, *J. Am. Chem. Soc.*, **72**, 3155 (1950).

⁴⁶ E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948).

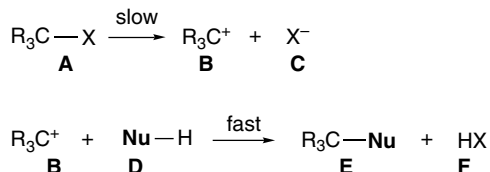
that exist along the reaction pathway. The sequence of reaction steps and intermediates involved in the overall transformation is the *reaction mechanism*. Reactants, intermediates, and products correspond to energy minima on the energy diagram and are separated by *activated complexes or transition states*, which are the molecular arrangements having the maximum energy for each successive step of the reaction mechanism. Figure 3.2 gives reaction energy diagrams for hypothetical reactions that proceed in one, two, or three steps through zero, one, or two intermediates. For the example in Figure 3.2, these are:



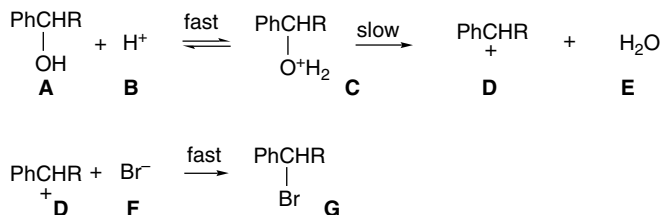
The diagram in (a), for example, might correspond to an S_N2 displacement reaction.



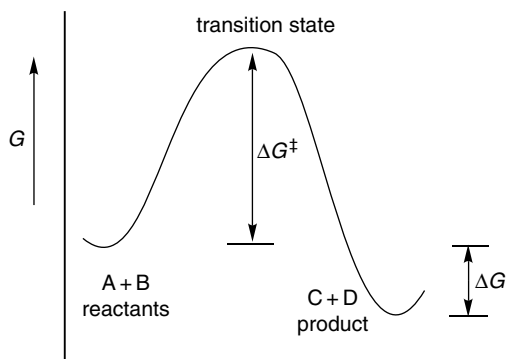
The diagram in (b) could pertain to an S_N1 reaction with a solvent **D** proceeding through a carbocation intermediate (**B**).



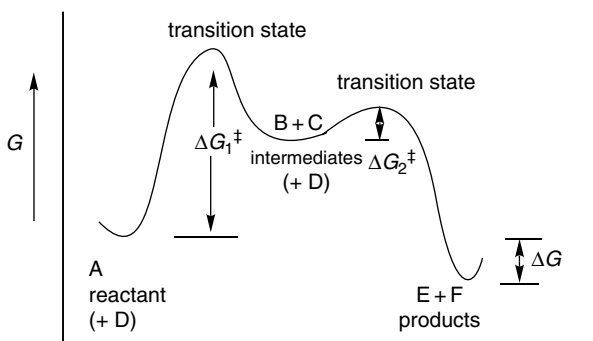
The diagram in (c) might apply to an acid-catalyzed ionization mechanism, such as might occur in a reaction of a secondary benzylic alcohol with HBr.



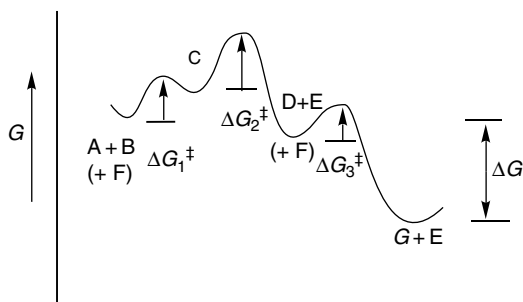
Such diagrams make clear the difference between an intermediate and a transition state. An intermediate lies in a depression on the potential energy curve. Thus, it has a finite lifetime, which depends on the depth of the depression. A shallow depression implies a low activation energy for the subsequent step, and therefore a short lifetime. The deeper the depression, the longer the lifetime of the intermediate. The situation at a transition state is quite different. This arrangement has only fleeting existence and represents an energy maximum on the reaction path.



(a) Energy diagram for a single-step reaction.



(b) Energy diagram for a two-step reaction.



(c) Energy diagram for a three-step reaction.

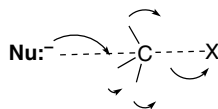
Fig. 3.2. Reaction energy profiles for one-, two-, and three-step reactions showing successive transition states and intermediates.

There is one path between reactants and products that has a lower energy maximum than any other and is the pathway that the reaction will follow. *The curve in a potential energy plot represents this lowest energy pathway.* It corresponds to a path across an energy surface describing energy as a function of the spatial arrangement of the atoms involved in the reaction. The progress of the reaction is called the *reaction coordinate*, and is a measure of the structural changes taking place as reaction occurs. The *principle of microscopic reversibility* arises directly from transition state theory. *The same pathway that is traveled in the forward direction of a*

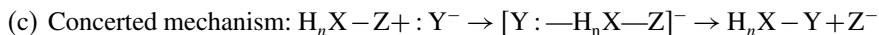
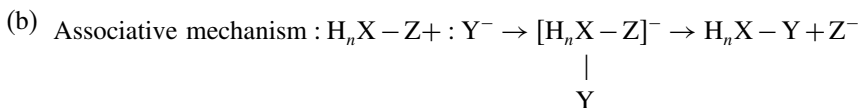
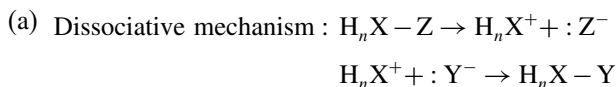
reaction will be traveled in the reverse direction, because it affords the lowest energy barrier for either process. Thus, information about the nature of a transition state or intermediate deduced by a study of a forward reaction is applicable to the reverse process occurring under the same conditions.

The overall rate of the reaction is controlled by the *rate-determining step*—the step that has the highest energy requirement and is the bottleneck for the overall process. In general, steps that occur after the rate-determining step do not enter into the overall rate equation for the reaction. In the example illustrated in Figure 3.2b, the first step is rate determining and the overall rate of the reaction would be given by the rate expression for the first step. In example (c), the second step is rate-determining.

3.2.2.2. Reaction Energy Diagrams with Two or More Dimensions. The reaction energy diagrams in Figure 3.2 depict reaction progress in terms of rupture and formation of the affected bonds. The reaction coordinate dimension represents the extent of completion of the bond-breaking/bond-making process. For example, in the S_N2 reaction shown in Figure 3.2a, the reaction coordinate corresponds to the trajectory for approach of the nucleophile and departure of the leaving group, but also implicitly includes the inversion of the carbon atom. The reaction coordinate can be expressed in terms of the **Nu**–C bond order, which begins as 0 at the left and proceeds to 1 when the reaction is complete.



Many reactions can usefully be described in terms of two-dimensional energy diagrams in which change in two different bonds are represented. For example, a nucleophilic substitution reaction at some element X (e.g., silicon) might occur by any of three general mechanisms:



The two-step mechanisms [(a) and (b)] represent paths along the edge of the two-dimensional reaction energy diagram, differing in the order of the two steps (Figure 3.3). The single-step (concerted) mechanism involves a more or less diagonal path with simultaneous bond breaking and bond making, as indicated by path C in Figure 3.3. These two-dimensional diagrams are often referred to as Albery-More

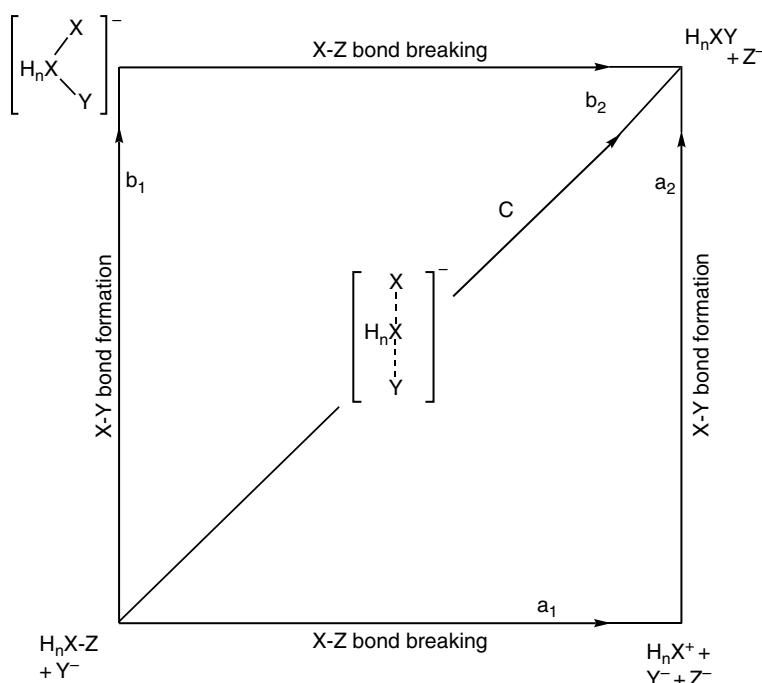
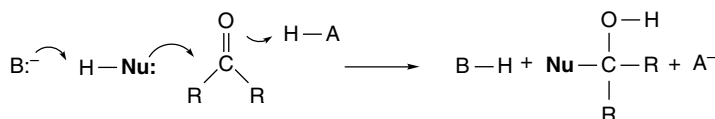


Fig. 3.3. Two-dimensional reaction energy diagram showing (a) dissociative, (b) associative, and (c) concerted mechanisms for a substitution reaction.

O’Ferrall-Jencks diagrams.⁴⁷ Energy is not explicitly shown in such diagrams, but it is a third dimension. We use such diagrams in the discussions of several reaction types, including elimination reactions (Section 5.10.1) and carbonyl addition reactions (Section 7.1). When the energy dimension is added, the diagram takes the form of a contour plot as shown in Figure 3.4. The preferred reaction pathway is over the lowest barrier.

Reactions involving changes at three bonds require a reaction cube and those with more bonding changes require cubes within cubes.⁴⁸ Figure 3.5 is a general representation of a reaction cube, and Figure 3.6 shows the cube corresponding to a reaction involving deprotonation of a nucleophile and protonation of a carbonyl oxygen in a carbonyl addition reaction.



Diagrams such as these can summarize the conclusions of kinetic and other studies of reaction mechanisms. Whether the diagram is in one, two, or three dimensions, it can specify the sequence of steps in the overall reaction.

⁴⁷ W. J. Albery, *Prog. React. Kinetics*, **4**, 353 (1967); R. A. More O’Ferrall, *J. Chem. Soc. B*, 274 (1970); W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

⁴⁸ E. Grunwald, *J. Am. Chem. Soc.*, **107**, 4715 (1985); P. H. Scudder, *J. Org. Chem.*, **55**, 4238 (1990); J. P. Guthrie, *J. Am. Chem. Soc.*, **118**, 12878 (1996).

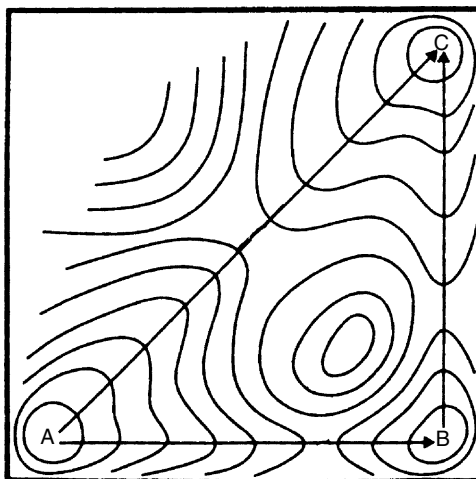


Fig. 3.4. Two-dimensional energy diagram showing energy contours for stepwise ($A \rightarrow B \rightarrow C$) and concerted ($A \rightarrow C$) reaction pathways.

3.2.2.3. Computation of Reaction Potential Energy Surfaces. As transition states cannot be observed, there is no experimental means of establishing their structure. Computational methods can be applied for descriptions of intermediates and transition structures. Structural attributes such as bond lengths, bond orders, electron density distribution, and orbital occupancy can be found for transition structures and intermediates, as was described in Sections 3.1.2.5 for stable molecules. The evaluation of a

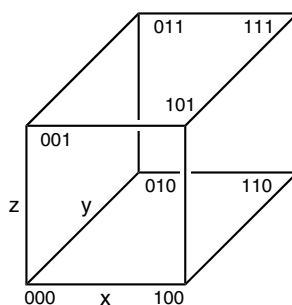


Fig. 3.5. Three-dimensional reaction coordinate diagram: x , y , and z are the three edge coordinates; $[0,0,0]$ is the starting point; $[1,1,1]$ is the product; $[1,0,0]$, $[0,1,0]$, and $[0,0,1]$ are the corner intermediates corresponding to reaction along only one edge coordinate; and $[1,1,0]$, $[1,0,1]$, and $[0,1,1]$ are the corner intermediates corresponding to the reaction along two edge coordinates. Reproduced with permission from *Can. J. Chem.*, **74**, 1283 (1996).

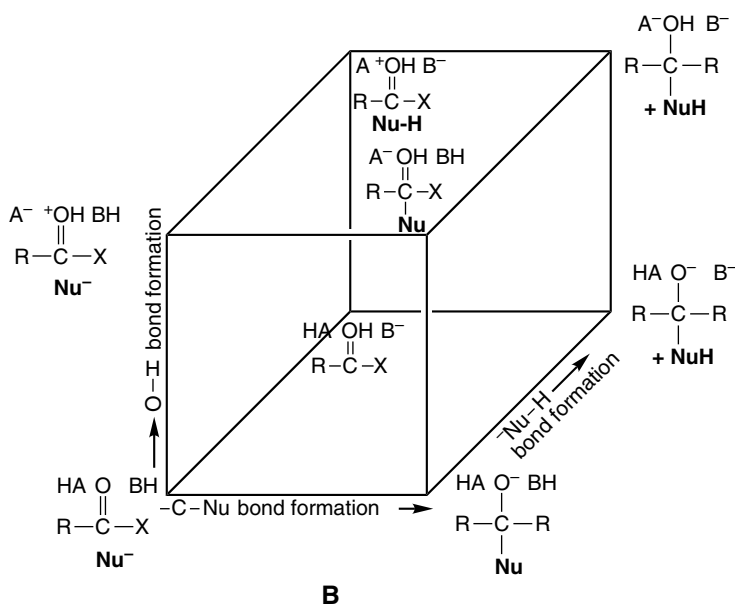


Fig. 3.6. Reaction progress cube showing possible intermediates for nucleophilic addition to a carbonyl group involving HA , B^- , and Nu-H . Adapted from *J. Org. Chem.*, **55**, 4238 (1990).

reaction mechanism typically involves the comparison of the energy of potential TSs. The expectation is that the reaction will proceed through the lowest energy TS, so if this can be reliably computed, the reaction mechanism can be defined. In the evaluation of stereoselectivity, for example, a comparison of the energies of the alternative TSs can predict the product ratio.

A very large number of structural variations can be conceived, but the structures of interest are the transition structures and intermediates that connect the reactants and products. The mathematics involved in characterizing a potential energy surface involves evaluation of energy gradients as a function of structural change. A *transition state* is a minimum in energy with respect to all changes in molecular dimensions except along the reaction coordinate, where it is a maximum on the energy surface. The transition state is a *saddle point*; that is, it is an energy minimum relative to change in any coordinate except in the direction of reaction. It is an energy maximum relative to that motion so the force constant is negative because there is no barrier to movement in that direction. A property of transition structures is that they have a *single imaginary vibrational frequency*, corresponding to the structural change in the direction of the reaction process. Because there are ordinarily many possible structural variations, the potential energy surface is a multidimensional hypersurface,⁴⁹ which can be described mathematically in terms of all the dimensions being explored. Because the reaction coordinate corresponds to the lowest-energy path, it can be located mathematically by minimization of the energy in all dimensions except that corresponding to the progress of the reaction. The computed minimum-energy path is called the *intrinsic reaction coordinate*.⁵⁰

⁴⁹. P. N. Skancke, *Acta Chem. Scand.*, **47**, 629 (1993).

⁵⁰. K. Fukui, *J. Phys. Chem.*, **74**, 4161 (1970); S. Kato and K. Fukui, *J. Am. Chem. Soc.*, **98**, 6395 (1976).

The calculation of the properties of transition structures is more problematic than for stable molecules because TSs involve bond breaking. Thus computations based on the concept of electron pairing may not be applicable, especially for species with radical character. Nevertheless, computational studies have provided insight into many reactions and we frequently use the results of these studies, as well as experimental work, in developing the details of reaction mechanisms.

3.2.3. Reaction Rate Expressions

Experimental kinetic data can provide detailed insight into reaction mechanisms. The rate of a given reaction can be determined by following the disappearance of a reactant or the appearance of a product. The extent of reaction is often measured spectroscopically, because spectroscopic techniques provide a rapid, continuous means of monitoring changes in concentration. Numerous other methods are available and may be preferable in certain cases. For example, continuous pH measurement or acid-base titration can be used to follow the course of reactions that consume or generate an acid or a base. Conductance measurements provide a means for determining the rate of reactions that generate ionic species; polarimetry can be used to follow reactions involving optically active materials. In general, any property that can be measured and quantitatively related to the concentration of a reactant or a product can be used to determine a reaction rate.

The goal of a kinetic study is to establish the quantitative relationship between the concentration of reactants and catalysts and the observed rate of the reaction. Typically, such a study involves rate measurements at enough different concentrations of each reactant to determine the *kinetic order* with respect to each reactant. A complete investigation allows the reaction to be described by a *rate expression* or *rate law*, which is an algebraic formula containing one or more *rate constants*, as well as terms for the concentration of all reactant species that are involved in the rate-determining and prior steps. Each concentration has an exponent called the *order of the reaction* with respect to that component. The overall kinetic order of the reaction is the sum of all the exponents in the rate expression. The mathematical form of the rate expression for a reaction depends on the order of the reaction. Using $[A_0]$, $[B_0]$, $[C_0]$, etc. for the initial ($t = 0$, t_0) concentrations and $[A]$, $[B]$, $[C]$, etc. as the reactant concentrations at time t , give the following expressions⁵¹:

FIRST ORDER: Rate = $k[A]$

$$\ln \frac{[A_0]}{[A]} = kt \quad \text{or} \quad [A] = [A]_0 e^{-kt} \quad (3.27)$$

SECOND ORDER/ONE REACTANT: Rate = $k[A]^2$

$$kt = \frac{1}{A} - \frac{1}{A_0} \quad (3.28)$$

SECOND ORDER/TWO REACTANTS: Rate = $k[A][B]$

$$kt = \frac{1}{[B_0] - [A_0]} \ln \frac{[A_0][B]}{[B_0][A]} \quad (3.29)$$

⁵¹. J. W. Moore and R. G. Pearson, *Kinetics and Mechanism*, 3rd Edition, John Wiley & Sons, New York, 1981, Chap. 2.

$$kt = \frac{1}{2} \left(\frac{1}{[A]^2} - \frac{1}{[A_0]^2} \right) \quad (3.30)$$

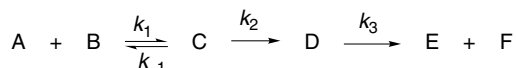
THIRD ORDER/TWO REACTANTS: Rate = $k[A]^2[B]$

$$kt = \frac{2}{(2[B_0] - [A_0])} \left(\frac{1}{[A]} - \frac{1}{[A_0]} \right) + \frac{2}{(2[B_0] - [A_0])^2} \ln \frac{[B_0][A]}{[A_0][B]} \quad (3.31)$$

Integrated expressions applicable to other systems are available.⁵²

The kinetic data available for a particular reaction are examined to determine if they fit a simple kinetic expression. For example, for a first-order reaction, a plot of $\log [A]$ versus t yields a straight line with a slope of $-k/2.303$. For second-order reactions, a plot of $1/[A]$ versus t is linear with a slope of k . Figure 3.7 shows such plots. Alternatively, the value of k can be calculated from the integrated expression over a sufficient time range. If the value of k remains constant, the data are consistent with that rate expression.

Many organic reactions consist of a series of steps involving several intermediates. The overall rate expression then depends on the relative magnitude of the rate constants for the individual steps. The relationship between a kinetic expression and a reaction mechanism can be appreciated by considering the several individual steps that constitute the overall reaction mechanism. The expression for the rate of any *single step* in a reaction mechanism contains a term for the concentration for each reacting species. Thus, for the reaction sequence:



the rates for the successive steps are:

$$\text{STEP 1: } \frac{d[C]}{dt} = k_1[A][B] - k_{-1}[C]$$

$$\text{STEP 2: } \frac{d[D]}{dt} = k_2[C]$$

$$\text{STEP 3: } \frac{d[E]}{dt} = \frac{d[F]}{dt} = k_3[D]$$

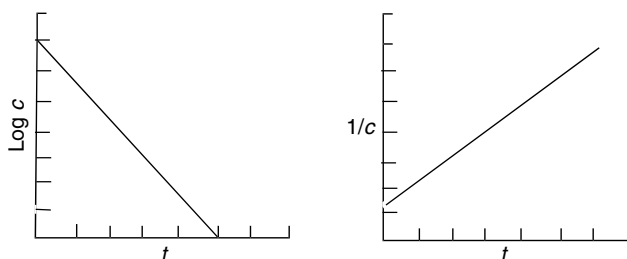


Fig. 3.7. Linear plots of $\log c$ versus t for a first-order reaction (a) and $1/c$ versus t for a second-order reaction.

⁵². C. Capellos and B. N. J. Bielski, *Kinetic Systems*, Wiley-Interscience, New York, 1972.

If we specify that the first step is a very rapid but unfavorable equilibrium, and that $k_2 \ll k_3$, then the second step is rate determining. Under these circumstances, the overall rate of the reaction will depend on the rate of the second step. In the reaction under consideration, the final step follows the rate-determining step and does not affect the rate of the overall reaction; k_3 does not appear in the overall rate expression. The rate of the reaction is governed by the second step, which is the bottleneck in the process. The rate of this step is equal to k_2 multiplied by the molar concentration of intermediate **C**, which is small and may not be measurable. It is therefore necessary to express the rate in terms of the concentration of reactants. In the case under consideration, this can be done by recognizing that **[C]** is related to **[A]** and **[B]** by an equilibrium constant:

$$K = \frac{[\text{C}]}{[\text{A}][\text{B}]}$$

Furthermore, K is related to k_1 and k_{-1} by the requirement that no net change in composition occur at equilibrium

$$k_{-1}[\text{C}] = k_1[\text{A}][\text{B}]$$

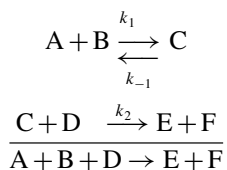
$$[\text{C}] = \frac{k_1}{k_{-1}}[\text{A}][\text{B}]$$

The rate of Step 2 can therefore be written in terms of **[A]** and **[B]**:

$$\frac{d[\text{D}]}{dt} = k_2[\text{C}] = k_2 \frac{k_1}{k_{-1}}[\text{A}][\text{B}] = k_{\text{obs}}[\text{A}][\text{B}]$$

Experimentally, it would be observed that the reaction rate would be proportional to both **[A]** and **[B]**. The reaction will be first order in each reactant and second order overall.

A useful approach that is often used in analysis and simplification of kinetic expressions is the *steady state approximation*, which can be illustrated by a hypothetical reaction scheme:



If **C** is a reactive, unstable species, its concentration will never be very large. It must be consumed at a rate that closely approximates the rate at which it is formed. Under these conditions, it is a valid approximation to set the rate of formation of **C** equal to its rate of destruction:

$$k_1[\text{A}][\text{B}] = k_2[\text{C}][\text{D}] + k_{-1}[\text{C}]$$

Rearrangement of this equation provides an expression for **[C]**:

$$\frac{k_1[\text{A}][\text{B}]}{(k_2[\text{D}] + k_{-1})} = [\text{C}]$$

By substituting into the rate for the second step, we obtain the following expression:

$$\text{Rate} = k_2[\text{C}][\text{D}] = k_2 \frac{k_1[\text{A}][\text{B}]}{(k_2[\text{D}] + k_{-1})}[\text{D}]$$

If $k_2[\text{D}]$ is much greater than k_{-1} , the rate expression simplifies to

$$\text{Rate} = \frac{k_2 k_1 [\text{A}][\text{B}][\text{D}]}{k_2 [\text{D}]} = k_1 [\text{A}][\text{B}]$$

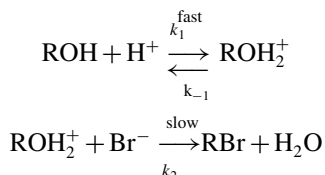
On the other hand, if $k_2[\text{D}]$ is much less than k_{-1} , the observed rate expression becomes

$$\text{Rate} = \frac{k_1 k_2 [\text{A}][\text{B}][\text{D}]}{k_{-1}}$$

The first situation corresponds to the first step being rate determining; in the second case, it is the second step, with the first step being a preequilibrium.

3.2.4. Examples of Rate Expressions

The normal course of a kinetic investigation involves the postulation of likely mechanisms and comparison of the observed rate expression with those expected for the various mechanisms. Those mechanisms that are incompatible with the observed kinetics can be eliminated as possibilities. One common kind of reaction involves proton transfer occurring as a rapid equilibrium preceding the rate-determining step, for example, in the reaction of an alcohol with hydrobromic acid to give an alkyl bromide:

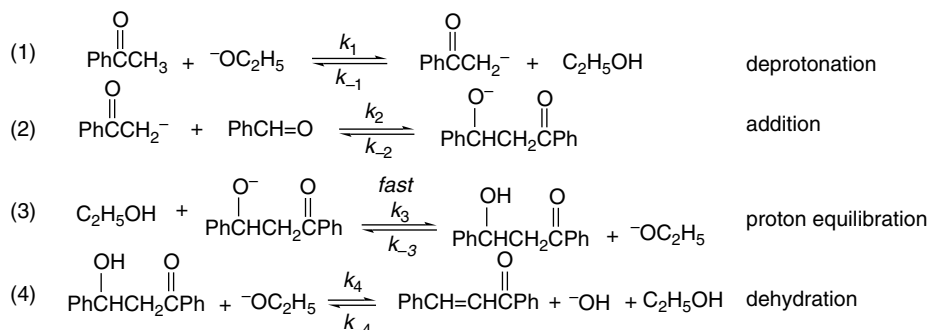


The overall rate being measured is that of Step 2, but there may be no means of directly measuring $[\text{ROH}_2^+]$. The concentration of the protonated intermediate ROH_2^+ can be expressed in terms of the concentration of the starting material by taking into consideration the equilibrium constant, which relates $[\text{ROH}]$, $[\text{Br}^-]$, and $[\text{H}^+]$:

$$\begin{aligned} K &= \frac{[\text{ROH}_2^+]}{[\text{ROH}][\text{H}^+]} \\ [\text{ROH}_2^+] &= K[\text{ROH}][\text{H}^+] \\ \text{Rate} &= k_2 K [\text{ROH}][\text{H}^+][\text{Br}^-] = k_{\text{obs}} [\text{ROH}][\text{H}^+][\text{Br}^-] \end{aligned}$$

To illustrate the development of a kinetic expression from a postulated reaction mechanism, let us consider the base-catalyzed reaction of benzaldehyde and acetophenone. Based on general knowledge of base-catalyzed reactions of carbonyl compounds, a reasonable sequence of steps can be written, but the relative rates of the steps is an open question. Furthermore, it is known that reactions of this type

are reversible, so the potential reversibility of each step must be taken into account. A completely reversible mechanism is as follows:



Because proton transfer reactions between oxygen atoms are usually very fast, Step 3 can be assumed to be a rapid equilibrium. With the above mechanism assumed, let us examine the rate expression that would result, depending upon which of the steps is rate determining. If Step 1 is rate controlling the rate expression would be

$$\text{Rate} = k_1[\text{PhCOCH}_3][^-\text{OC}_2\text{H}_5]$$

Under these conditions the concentration of the second reactant, benzaldehyde, would not enter into the rate expression. If Step 1 is an equilibrium and Step 2 is rate controlling, we obtain the rate expression

$$\text{Rate} = k_2[\text{PhCOCH}_2^-][\text{PhCHO}]$$

which on substituting in terms of the prior equilibrium gives

$$\text{Rate} = k_2 K_1[\text{PhCOCH}_3][^-\text{OC}_2\text{H}_5][\text{PhCHO}]$$

since

$$[\text{PhCOCH}_2^-] = K_1[\text{PhCOCH}_3][^-\text{OC}_2\text{H}_5]$$

where K_1 is the equilibrium constant for the deprotonation in the first step. If the final step is rate controlling the rate is

$$\text{Rate} = k_4[\text{PhCH(OH)CH}_2\text{COPh}][^-\text{OC}_2\text{H}_5]$$

The concentration of the intermediate $\text{PhCH(OH)CH}_2\text{COPh}$ (**I**) can be expressed in terms of the three prior equilibria. Using **I** for the intermediate and I^- for its conjugate base and neglecting $[\text{EtOH}]$, since it is the solvent and will remain constant, gives the following relationships:

$$K_3 = \frac{[\text{I}][^-\text{OEt}]}{[\text{I}^-]} \quad \text{and} \quad [\text{I}] = K_3 \frac{[\text{I}^-]}{[^-\text{OEt}]}$$

Substituting for $[\text{PhCOCH}_2^-]$ from the equilibrium expression for Step 1 gives

$$[\text{I}] = \frac{K_3 K_2 [\text{PhCHO}]}{[\text{OEt}^-]} K_1 [\text{PhCOCH}_3] [\text{OEt}^-] = K' [\text{PhCHO}] [\text{PhCOCH}_3]$$

This provides the final rate expression:

$$\text{Rate} = k_{\text{obs}} [\text{OC}_2\text{H}_5] [\text{PhCHO}] [\text{PhCOCH}_3]$$

Note that the form of this third-order kinetic expression is identical to that in the case where the second step was rate determining and would not distinguish between the two possibilities.

Experimental studies of this base-catalyzed condensation have revealed that it is third order, indicating that either the second or fourth step must be rate determining. Studies on the intermediate **I** obtained by an alternative synthesis have shown that k_4 is about four times as large as k_3 so that about 80% of **I** goes on to product. These reactions are faster than the overall reaction under the same conditions, so the second step must be rate controlling.⁵³

These examples illustrate the relationship between kinetic results and the determination of the reaction mechanism. Kinetic results can exclude from consideration all mechanisms that require a rate law different from the observed one. It is often true, however, that related mechanisms give rise to identical predicted rate expressions. In that case, the mechanisms are *kinetically equivalent* and a choice between them is not possible solely on the basis of kinetic data. A further limitation on the information that kinetic studies provide should also be recognized. Although the data can give the *composition* of the activated complex for the rate-determining and preceding steps, it provides no information about the *structure* of the activated complex or any intermediates. Sometimes the structure can be inferred from related chemical experience, but it is never established solely by kinetic data.

3.3. General Relationships between Thermodynamic Stability and Reaction Rates

We have considered the fundamental principles of thermodynamics and reaction kinetics. Now we would like to search for relationships between stability, as defined by thermodynamics, and reactivity, which is described by kinetics. Reaction potential energy diagrams are key tools in making these connections.

3.3.1. Kinetic versus Thermodynamic Control of Product Composition

Product composition at the end of the reaction may be governed by the equilibrium thermodynamics of the system. When this is true, the product composition is governed by *thermodynamic control* and the stability difference between the competing products, as given by the free-energy difference, determines the product composition. Alternatively, product composition may be governed by competing rates of formation of

⁵³. E. Coombs and D. P. Evans, *J. Chem. Soc.*, 1295 (1940); D. S. Noyce, W. A. Pryor, and A. H. Bottini, *J. Am. Chem. Soc.*, **77**, 1402 (1955).

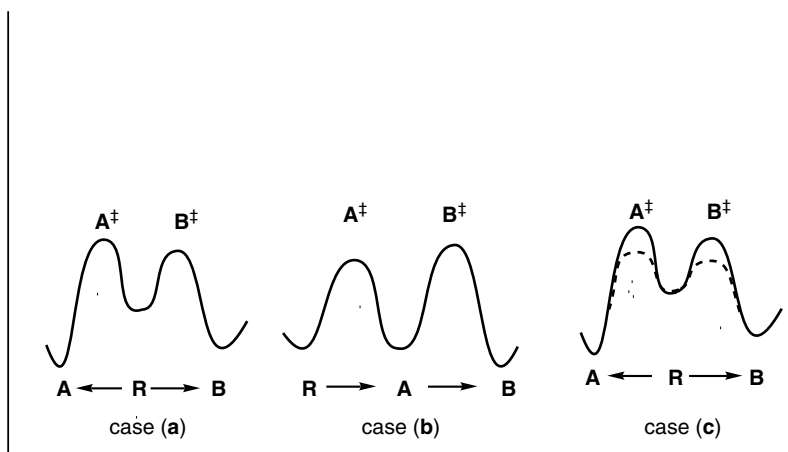


Fig. 3.8. Examples of reactions under kinetic and thermodynamic control. (a) $\Delta G_B^\ddagger < \Delta G_A^\ddagger$; (b) $\Delta G_A^\ddagger < \Delta G_B^\ddagger$; (c) alternative mechanism for product equilibrium.

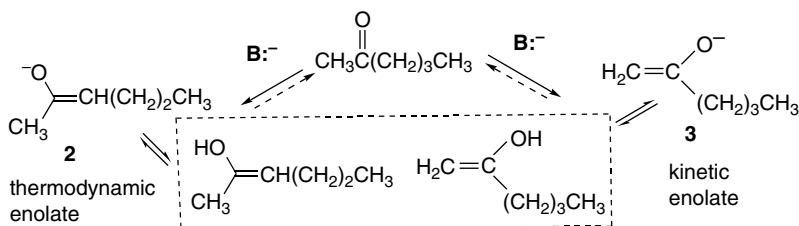
products, which is called *kinetic control*. Let us consider cases (a) to (c) in Figure 3.8. In case (a), the ΔG^\ddagger 's for formation of the competing transition states A[‡] and B[‡] from the reactant R are substantially less than the ΔG^\ddagger 's for formation of A[‡] and B[‡] from A and B, respectively. If the latter two ΔG^\ddagger 's are sufficiently large that the competitively formed products B and A do not return to R, the ratio of the products A and B at the end of the reaction will not depend on their relative stabilities, but only on the *relative rates of formation*. The formation of A and B is effectively irreversible in these circumstances. The reaction energy profile in case (a) corresponds to this situation and is a case of kinetic control. The relative amounts of products A and B depend on the relative activation barriers ΔG_A^\ddagger and ΔG_B^\ddagger and not on the relative stability of products A and B. The diagram shows $\Delta G_B^\ddagger < \Delta G_A^\ddagger$, so the major product will be B, even though it is less stable than A.

Case (b) represents a situation of two successive reactions. The lowest ΔG^\ddagger is that for formation of A[‡] from R. But, the ΔG^\ddagger for formation of B[‡] from A is not much larger. The system in (b) might be governed by either kinetic or thermodynamic factors. Conversion of R to A will be only slightly faster than conversion of A to B. If the reaction conditions are carefully adjusted it will be possible for A to accumulate and not proceed to the more stable product B. Under such conditions, A will be the dominant product and the reaction will be under kinetic control. Under somewhat more energetic conditions, for example, at a higher temperature, A will be transformed into B. Under these conditions the reaction will be under thermodynamic control. A and B will equilibrate and the product ratio will depend on the equilibrium constant determined by ΔG for the reaction $A \rightleftharpoons B$.

In case (c), the solid reaction energy profile represents the same situation of kinetic control as shown in (a), with product B (which is thermodynamically less stable) being formed because $\Delta G_B^\ddagger < \Delta G_A^\ddagger$. The dashed energy profile represents a different set of conditions for the same transformation, such as addition of a catalyst or change of solvent, that substantially reduces the energy of A[‡] and B[‡] such that interconversion of A and B is fast. This will result in formation of the more stable product A, even though the barrier to formation of B remains lower. Under these circumstances, the reaction is under *thermodynamic control*.

Thus, whenever competing or successive reaction products can come to equilibrium, the product composition will reflect relative stability and be subject to thermodynamic control. If product composition is governed by competing rates, the reaction is under kinetic control. A given reaction may be subject to either thermodynamic or kinetic control, depending on the conditions.

The idea of kinetic versus thermodynamic control can be illustrated by a brief discussion of the formation of enolate anions from unsymmetrical ketones. This is a very important matter for synthesis and is discussed more fully in Chapter 6 and in Section 1.1.2 in Part B. Most ketones can give rise to more than one enolate. Many studies have shown that the ratio among the possible enolates that are formed depends on the reaction conditions.⁵⁴ This can be illustrated for the case of 2-hexanone. If the base chosen is a strong, sterically hindered one, such as lithium diisopropylamide, and the solvent is aprotic, the major enolate formed is **3** in the diagram below. If a protic solvent or a weaker base (one comparable in basicity to the ketone enolate) is used, the dominant enolate is **2**. Under these latter conditions, equilibration can occur by reversible formation of the enol. Enolate **3** is the kinetic enolate, but **2** is thermodynamically favored.



The structural and mechanistic basis for the relationships between kinetic versus thermodynamic control and the reaction conditions is as follows. The α -hydrogens of the methyl group are less sterically hindered than the α -hydrogens of the butyl group. As a result, removal of a methyl hydrogen as a proton is faster than removal of a butyl hydrogen. This effect is magnified when the base is sterically bulky and is particularly sensitive to the steric environment of the competing hydrogens. If the base is very strong, the enolate will not be reconverted to the ketone because the enolate is too weak a base to regain the proton. These conditions correspond to (a) in Figure 3.8 and represent a case of kinetic control. If a weaker base is used or if the solvent is protic, protons can be transferred reversibly between the isomeric enolates and the base (because the base strengths of the enolate and the base are comparable). Under these conditions the more stable enolate will be dominant because the enolates are in equilibrium. The more substituted enolate **2** is the more stable of the pair, just as more substituted alkenes are more stable than terminal alkenes. This corresponds to case (c) in Figure 3.8, and product (enolate) equilibration occurs through rapid proton exchange. In protic solvents this exchange can occur through the enols.

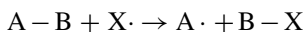
3.3.2. Correlations between Thermodynamic and Kinetic Aspects of Reactions

Is there any inherent relationship between the free energy of a reaction, ΔG , and the rate of reaction, which is governed by ΔG^\ddagger ? Are more exothermic reactions

⁵⁴ J. d'Angelo, *Tetrahedron*, **32**, 2979 (1976); H. O. House, *Modern Synthetic Reactions*, 2nd Edition, W. A. Benjamin, Menlo Park, CA, 1972.

faster? These questions raise the issue of a relationship between the thermodynamic and kinetic aspects of reactivity. It turns out that there frequently are such relationships *in series of closely related reactions*, although there is no fundamental requirement that this be the case. The next several sections discuss examples of such relationships.

3.3.2.1. Bell-Evans-Polyani Relationship. The Bell-Evans-Polyani formula deals with the relationship between reaction rate and exothermicity for a series of related single-step reactions.⁵⁵ Evans and Polyani pointed out that for a series of homolytic atom transfer reactions of the general type

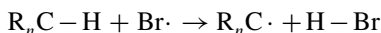


there was a relationship between the activation energy and the reaction enthalpy, which can be expressed as

$$E_a = E_0 + \alpha\Delta H \quad (3.32)$$

where E_0 is the activation energy of the reference reaction and ΔH is the enthalpy of each reaction in the series. In terms of reaction energy diagrams, this indicates that for reactions having similar energy profiles, the height of the barrier will decrease as the reaction becomes more exothermic (and vice versa), as illustrated in Figure 3.9.

This relationship can be explored, for example, by considering the rates of hydrogen abstraction reactions. For example, the E_a for hydrogen abstraction from simple hydrocarbons⁵⁶ shown below can be compared with the ΔH of the reaction, as derived from the bond energy data in Table 3.2. The plot is shown in Figure 3.10.



Alkane	E_a	ΔH
CH ₃ -H	18.3	+18.0
C ₂ H ₅ -H	13.4	+13.5
(CH ₃) ₂ CH-H	10.2	+11.1
C ₂ H ₅ CH(CH ₃)-H	10.2	+11.3
(CH ₃) ₃ C-H	7.5	+8.7



Fig. 3.9. Energy profiles for series of related reactions illustrating the Bell-Evans-Polyani relationship.

⁵⁵ M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **34**, 11 (1938).

⁵⁶ G. C. Fettes and A. F. Trotman-Dickenson, *J. Am. Chem. Soc.*, **81**, 5260 (1959).

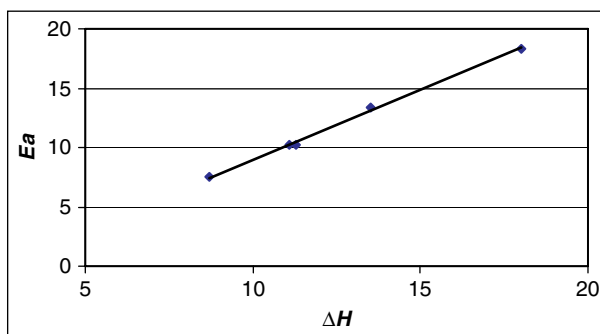


Fig. 3.10. Plot of E_a for abstraction of hydrogen from alkanes by bromine atom versus ΔH .

Another example of data of this type pertains to the reaction of *t*-butoxy radicals with hydrocarbons.⁵⁷ The *t*-butoxy radical is more reactive and less selective than bromine atoms and the E_a are quite low. There is a correlation corresponding to Equation (3.32), with $\alpha = 0.3$ for hydrocarbons with C–H bond strengths greater than ~ 90 kcal/mol. For weaker bonds, the E_a levels off at about 2 kcal/mol. We say more about the relationship between E_a for hydrogen abstraction and the enthalpy of the reaction in Topic 11.2.

Hydrocarbon	BDE (kcal/mol)	E_a (kcal/mol)
Triphenylmethane	81	1.9
Diphenylmethane	84	2.4
3-Phenylpropene	82	2.5
Toluene	90	3.5
Cyclopentane	97	3.5
Cyclohexane	99	4.4
<i>t</i> -Butylbenzene	101	6.1

3.3.2.2. Hammond's Postulate. Because the rates of chemical reactions are controlled by ΔG^\ddagger , information about the structure of TSs is crucial to understanding reaction mechanisms. However, because TSs have only transitory existence, it is not possible to make experimental measurements that provide direct information about their structure. Hammond pointed out the circumstances under which it is valid to relate transition state structure to the structure of reactants, intermediates, or products.⁵⁸ His statement is known as *Hammond's postulate*. Discussing individual steps in a reaction mechanism, Hammond's postulate states: "*If two states, as, for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of molecular structure.*"

This statement can be discussed with reference to potential energy diagrams. Case (a) in Figure 3.11 represents a very exothermic step with a low activation energy. It follows from Hammond's postulate that in this step, the TS will resemble the reactant, because the two are close in energy and interconverted by a small structural

⁵⁷. M. Finn, R. Fridline, N. K. Suleman, C. J. Wohl, and J. M. Tanko, *J. Am. Chem. Soc.*, **126**, 7578 (2004).

⁵⁸. G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

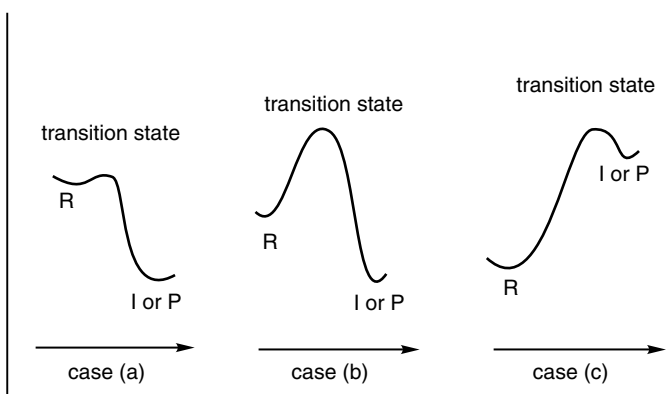
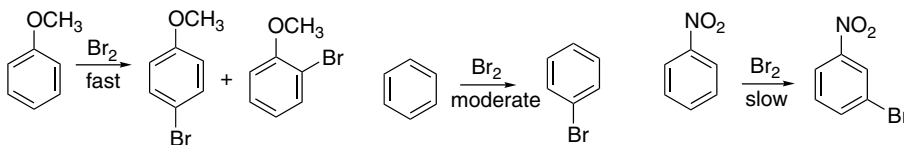


Fig. 3.11. Reaction energy diagram illustrating Hammond's postulate: (a) early transition structure resembles reactant, (b) midpoint transition structure resembles neither reactant or product, (c) late transition structure resembles intermediate or product.

change. This is depicted in the potential energy diagram as a small displacement toward product along the reaction coordinate. This means that comparisons between closely related series of reactants should depend primarily on *structural features present in the reactant*. Case (b) describes a step in which the energy of the TS is a good deal higher than either the reactant or the product. In this case, neither the reactant nor the product is a good model of the TS. Independent information is needed to postulate the characteristics of the TS. Comparison among a series of reactants should focus primarily on TS structure. Case (c) illustrates an endothermic step, such as might occur in the formation of an unstable intermediate. In this case the energy of the TS is similar to that of the intermediate and the TS should be similar in structure to the intermediate. Structural and substituent effects can best be interpreted in terms of their effect on the stability of the intermediate.

The significance of the concept incorporated in Hammond's postulate is that in appropriate cases it permits discussion of TS structure in terms of the reactants, intermediates, or products in a multistep reaction sequence. The postulate indicates that the cases where such comparison is appropriate are those in which the TS energy is close to that of the reactant, intermediate, or product. Chemists sometimes speak of an "early" or "late" TS. An "early" TS is reactant-like, whereas a "late" TS is intermediate- (or product-) like.

Electrophilic aromatic substitution is a situation in which it is useful to discuss TS structure in terms of a reaction intermediate. The *ortho*, *para*, and *meta* directing effects of aromatic substituents were among the first structure-reactivity relationships to be developed in organic chemistry. Certain functional groups activate aromatic rings toward substitution and direct the entering electrophile to the *ortho* and *para* positions, whereas others are deactivating and lead to substitution in the *meta* position. The bromination of methoxybenzene (anisole), benzene, and nitrobenzene can serve as examples for discussion.



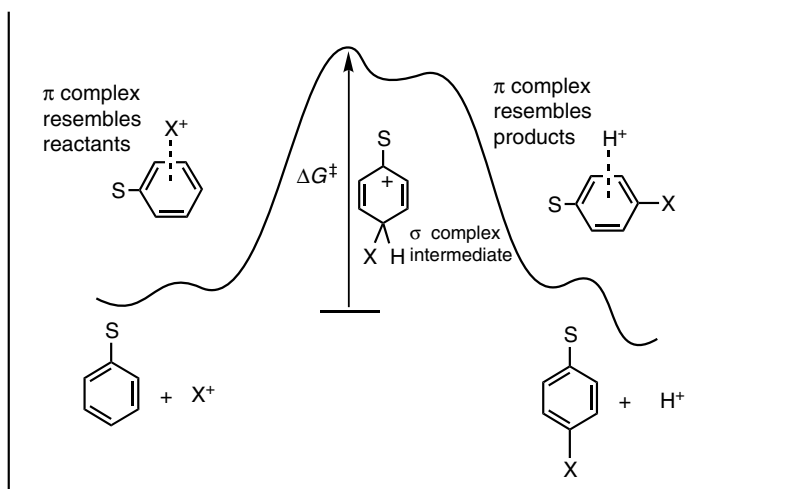
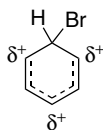


Fig. 3.12. Potential energy diagram for electrophilic aromatic substitution.

It can be demonstrated that the reactions are kinetically controlled; that is, there is no isomerization among the *ortho*, *meta*, and *para* products after they are formed. It is therefore the ΔG^\ddagger values that hold the key to the connection between the rate effects and the substituent-directing effects. However, to discuss the effect of substituents on ΔG^\ddagger , we must know something about the reaction mechanism and the nature of the competing TS. Electrophilic aromatic substitution is dealt with in detail in Chapter 9. Evidence presented there indicates that electrophilic aromatic substitution involves a distinct intermediate and two less well-defined states. The potential energy diagram in Figure 3.12 is believed to be a good representation of the energy changes that occur during bromination. By application of the Hammond postulate, we conclude that the rate-determining step involves formation of a TS that closely resembles the intermediate, which is called the “ σ complex.” It is therefore appropriate to discuss the effect of substituents on the TS in terms of the structure of this intermediate.

Because the product composition is kinetically controlled, the isomer ratio is governed by the relative magnitudes of ΔG_o^\ddagger , ΔG_m^\ddagger , and ΔG_p^\ddagger , the energies of activation for the *ortho*, *meta*, and *para* transition states, respectively. Figure 3.13 shows a qualitative comparison of these ΔG^\ddagger values. At the TS, a positive charge is present on the benzene ring, primarily at positions 2, 4, and 6 in relation to the entering bromine.



The electron-releasing methoxy group interacts directly to delocalize the charge and stabilize the intermediates leading to *o*- and *p*-bromination, but does not stabilize the intermediate leading to *m*-substitution product.

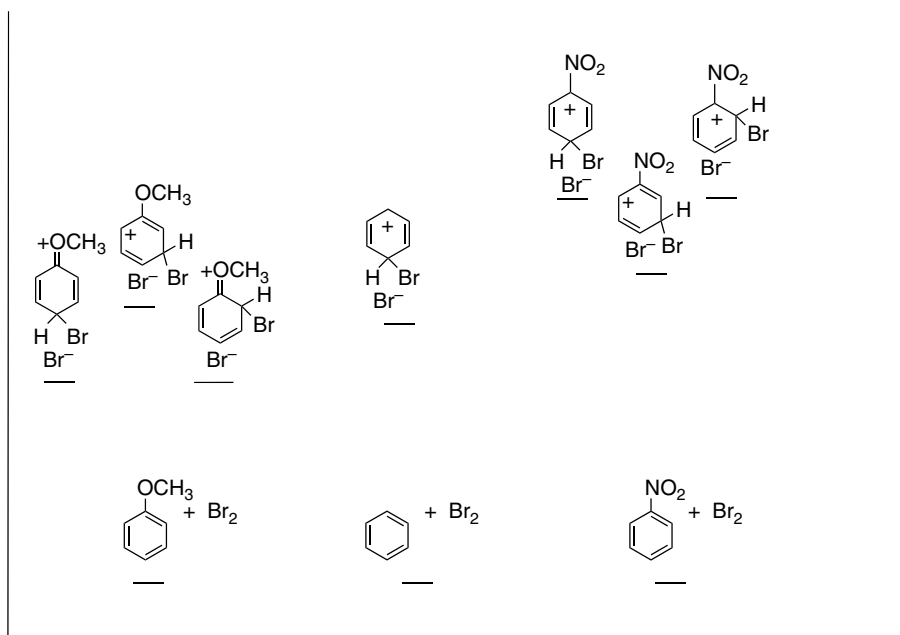
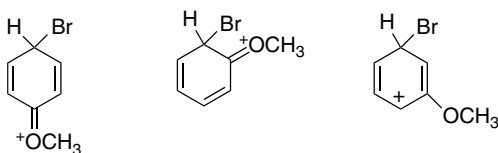
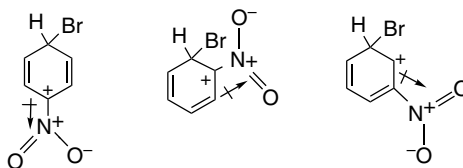


Fig. 3.13. Relative energies of intermediates for bromination of methoxybenzene, benzene, and nitrobenzene indicating the effect of substituents on energy of intermediates.



The *o*- and *p*-intermediates are therefore stabilized relative to benzene but the *m*-intermediate is not, as is illustrated in Figure 3.13. As a result, methoxybenzene reacts faster than benzene and the product is mainly the *o*- and *p*-isomers.

In the case of nitrobenzene, the electron-withdrawing nitro group cannot stabilize the positive charge in the σ -complex intermediate. In fact, it strongly destabilizes the intermediate as a result of an unfavorable polar interaction. This destabilization is greatest in the *o*- and *p*-intermediates, which place a partial positive charge on the nitro-substituted carbon. The *meta*-TS is also destabilized relative to benzene, but not as much as the *ortho*- and *para*-TS. As a result nitrobenzene is less reactive than benzene and the product is mainly the *meta*-isomer



The substituent effects in aromatic electrophilic substitution are dominated by *resonance effects*. In other systems, stereoelectronic or steric effects might be more

important. Whatever the nature of the substituent effects, the Hammond postulate recognizes that structural discussion of transition states in terms of reactants, intermediates, or products is valid only when their structures and energies are similar.

3.3.2.3. The Marcus Equation. The *Marcus equation* provides a means for numerical evaluation of the relationship between ΔG° and ΔG^\ddagger . The Marcus equation proposes that for a single-step reaction process there is a relationship involving the net exo- or endothermicity of the reaction and an energy associated with the activation process called the *intrinsic barrier*.⁵⁹ The Marcus equation proposes that for a series of related reactions, there is a predictable relationship between ΔG^\ddagger and ΔG° , the free energy of reaction. The energies of the reactants, transition state, and products can be described by intersecting parabolic potential energy functions. The relationship can be expressed by the following equation:

$$\Delta G^\ddagger = \tilde{G}[1 + (\Delta G^\circ/4\tilde{G})]^2 \quad (3.33)$$

where \tilde{G} is the intrinsic barrier of the reaction and ΔG° and ΔG^\ddagger are free energy and energy of activation for the reaction under consideration.

The Marcus equation (3.33), like the Bell-Evans-Polyani relationship, indicates that for a related series of reactions, the activation energy (and therefore the rate) is related to the net free-energy change. It is based on assumption of a parabolic shape of the potential energy curve and breaks down at certain limits. The range of the equation can be extended by other formulations of the shape of the potential energy functions.⁶⁰ Figure 3.14 plots a series of reaction energy profiles with $\tilde{G} = 25$ kcal and ΔG° varying

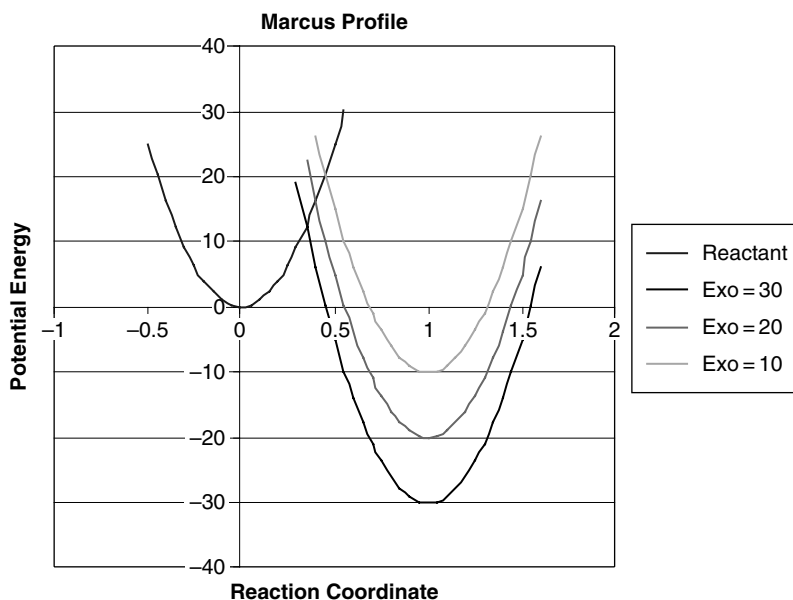


Fig. 3.14. Marcus equation plots for a hypothetical reaction series with an intrinsic barrier of 25 kcal/mol and exothermicities of 10, 20, and 30 kcal/mol.

⁵⁹ R. A. Marcus, *J. Phys. Chem.*, **72**, 891 (1968); R. A. Marcus, *J. Am. Chem. Soc.*, **91**, 7224 (1969).

⁶⁰ E. S. Lewis, C. S. Shen, and R. A. More O'Ferrall, *J. Chem. Soc., Perkin Trans.*, **2**, 1084 (1981).

from 0 to -30 kcal/mol, and it illustrates that we can indeed expect a correlation between reaction exothermicity (or endothermicity) and rate. The Marcus equation makes another prediction that is quite surprising—that the barrier will increase again for very exothermic reactions. This is called the *inverted region*. This aspect of Marcus theory is not widely applied in organic chemistry, but is of considerable importance in electron transfer reactions.

The Marcus equation can be modified to Equation (3.34) to take account of other energy changes, for example, the desolvation and electrostatic interactions that are involved in bringing together the ensemble of reacting molecules. These energies contribute to the observed activation energy. Similarly, there may be residual interactions in the product ensemble that differ from the independent molecules.⁶¹ Guthrie proposed the following equations:

$$\Delta G_{\text{corr}} = \tilde{G} \left(1 + \frac{\Delta G_{\text{corr}}^{\circ}}{4\tilde{G}} \right)^2 \quad (3.34)$$

$$\Delta G_{\text{corr}}^{\ddagger} = \Delta G_{\text{obs}}^{\ddagger} - W_R \quad (3.35)$$

$$\Delta G_{\text{corr}}^{\circ} = \Delta G_{\text{obs}}^{\circ} + W_R - W_P \quad (3.36)$$

where W_R is work to bring reactants together and W_P is work to bring products together. In this formulation, the assignment of W_R and W_P terms, which includes solvation, requires careful consideration. Figure 3.15 shows a reaction energy diagram including the W_R and W_P terms.

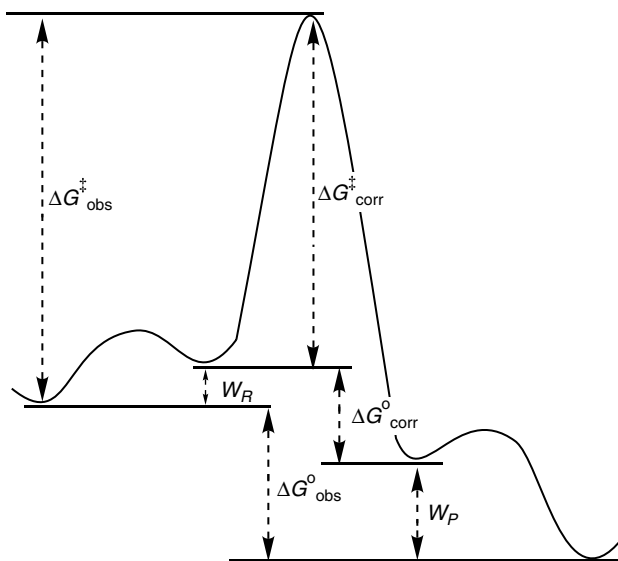
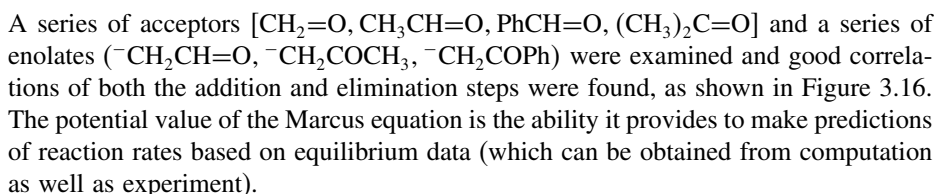
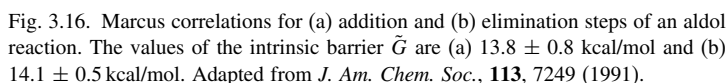


Fig. 3.15. Model for a reaction, $A + B \rightleftharpoons A \cdots B \rightleftharpoons C \cdots D \rightleftharpoons C + D$ used in applying the Marcus theory. The reactants come together in an encounter complex (A,B) at a free-energy cost W_R and react within this complex to form (C,D), the encounter complex of products, which then separate, releasing free energy W_P . The Marcus theory applies to reactions within the encounter complex where $\Delta G_{\text{corr}}^{\ddagger}$ is determined by $\Delta G_{\text{corr}}^{\circ}$ and the intrinsic barrier \tilde{G} . Reproduced from *Can. J. Chem.*, **74**, 1283 (1996), by permission from National Research Council Press.

⁶¹ J. P. Guthrie, *Can. J. Chem.*, **74**, 1283 (1996).



The Bell-Evans-Polanyi relationship, Hammond's postulate, and the Marcus equation are all approaches to analyzing, understanding, and predicting relationships between the thermodynamics and kinetics of a series of closely related reactions. This is an important issue in organic chemistry, where series of reactions differing only in peripheral substituents are common. Each of these approaches provides a sound basis for the intuitive expectation that substituents that favor a reaction in a thermodynamic

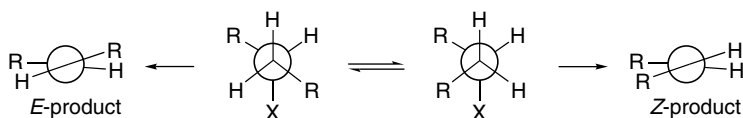


⁶². J. P. Guthrie, *J. Am. Chem. Soc.*, **113**, 7249 (1991).

sense will also do so in a kinetic sense. Each of these approaches pertains to series of reactions that proceed by *similar mechanisms*, because they are based upon a series of closely related reaction energy profiles. If substituents have a strong enough effect to change the mechanism, for example, a change in the rate-determining step, the relationships cannot be expected to hold.

3.3.3. Curtin-Hammett Principle.

In Chapter 2, we discussed conformational equilibria of organic molecules. At this point, let us consider how conformational equilibria can affect chemical reactivity. Under what circumstances can the position of the conformational equilibrium for a reactant determine which of two competing reaction paths will be followed? A potential energy diagram is shown in Figure 3.17. It pertains to a situation where one conformation of a reactant would be expected to give product A and another product B. This might occur, for example, in a stereospecific *anti* elimination.



In most cases, the energy of activation for a chemical reaction is greater than that for a conformational equilibration, as is illustrated in the Figure 3.17. If this is the case, ΔG_a^\ddagger and $\Delta G_b^\ddagger \gg \Delta G_c$. The conformers of the reactant are in equilibrium and are interconverted at a rate much faster than the competing reactions occur.

According to transition state theory,

$$k_r = \frac{\kappa k_B T}{h} e^{\Delta G^\ddagger / RT} \quad \text{and} \quad K_c = e^{\Delta G_c / RT} \quad (3.37)$$

$$\text{Product ratio} = \frac{(\kappa k_B T / h) e^{-\Delta G_a^\ddagger / RT} e^{+\Delta G_c / RT}}{(\kappa k_B T / h) e^{-\Delta G_b^\ddagger / RT}} \quad (3.38)$$

$$= e^{(-\Delta G_a^\ddagger + \Delta G_b^\ddagger + \Delta G_c) / RT} \quad (3.39)$$

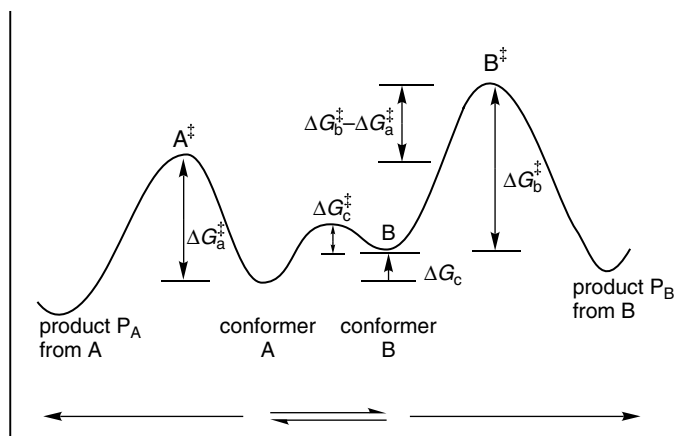


Fig. 3.17. Reaction potential energy diagram illustrating the Curtin-Hammett principle.

$$\Delta G_b^\ddagger - \Delta G_a^\ddagger + \Delta G_c = G_b^\ddagger - G_a^\ddagger \quad (3.40)$$

The product ratio is therefore not determined by ΔG_c but by the relative energy of the two transition states A^\ddagger and B^\ddagger . The conclusion that the ratio of products formed from conformational isomers is not determined by the conformational equilibrium ratio is known as the *Curtin-Hammett principle*.⁶³ Although the rate of the formation of the products is dependent upon the relative concentration of the two conformers, because ΔG_b^\ddagger is decreased relative to ΔG_a^\ddagger to the extent of the difference in the two conformational energies, the conformational preequilibrium is established rapidly, relative to the two competing product-forming steps.⁶⁴ The position of the conformational equilibrium cannot control the product ratio. The reaction can proceed through a minor conformation if it is the one that provides access to the lowest-energy transition state.

The same arguments can be applied to other energetically facile interconversions of two potential reactants. For example, some organic molecules can undergo rapid proton shifts (tautomerism) and the chemical reactivity of the two isomers may be quite different. However, it is not valid to deduce the ratio of two tautomers on the basis of subsequent reactions that have activation energies greater than that of the tautomerism. Just as in the case of conformational isomerism, the ratio of products formed in subsequent reactions is not controlled by the position of the facile equilibrium, but by the E_a of the competing steps.

3.4. Electronic Substituent Effects on Reaction Intermediates

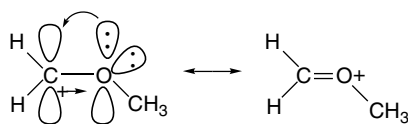
It is often observed that the introduction of substituents changes the rate of organic reactions, even if the substituent is not directly involved in the reaction. Changes that affect the ΔG^\ddagger for the rate-determining, or preceding, steps will cause a change in the observed reaction rate. The difference can result from energy changes in the reactant(s) or transition state, or both. Shifts in product composition can result from changes in the relative ΔG^\ddagger of competing reaction paths. In the broadest terms, there are three kinds of substituent effects, resulting from electronic, steric, and structure-specific interactions. *Steric effects* have their origin in nonbonding interactions. *Structure-specific interactions* include, for example, intramolecular hydrogen bonding and neighboring-group participation that depend on location of the substituents that are involved. In this section, we focus on *electronic effects*. Electronic substituent effects can be further subdivided. Substituents can operate by delocalization of electrons by *resonance* or *hyperconjugation*, including $\sigma - \sigma^*$ and $\sigma - \pi^*$, as well as $\pi - \pi$ delocalization. Resonance and hyperconjugation operate through specific orbital interactions and therefore impose particular *stereoelectronic* requirements; that is, interacting orbitals must be correctly aligned. *Polar effects* are electrostatic and include both the effect of proximate charges owing to bond dipoles and the effects of more distant centers of charge. Polar effects also may have a geometric component. For example, the orientation of a particular bond dipole determines how it interacts with a developing charge at a reaction center elsewhere in the molecule. Polar effects are

⁶³ D. Y. Curtin, *Rec. Chem. Prog.*, **15**, 111 (1954); E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, pp. 151–152, 237–238.

⁶⁴ For a more complete discussion of the relationship between conformational equilibria and reactivity, see J. I. Seeman, *Chem. Rev.*, **83**, 83 (1983).

sometimes subdivided into *inductive* and *field effects*. Effects attributed to proximate electronic changes owing to bond dipoles are called inductive effects and those that are due to dipole interaction through space are called field effects. *Polarizability effects*, which result from distortion of electronic distribution of a group, provide another mechanism of substituent interaction, and can be particularly important in the gas phase.

The broad classification of substituents into electron-releasing groups (ERGs) and electron-withdrawing groups (EWGs) is useful. However, to achieve further refinement, we must make two additional distinctions. *The electronic effects of substituents resulting from delocalization and polar interactions are not necessarily in the same direction.* A methoxy substituent on a carbocation is a good example. The oxygen atom is strongly stabilizing by resonance because it permits a π bond to form between oxygen and carbon, thereby delocalizing the positive charge. However, the C–O bond dipole is destabilizing, since it increases the positive charge at carbon. In this case the resonance stabilizing effect is dominant and the carbocation is strongly stabilized (see p. 21–22).



We also have to recognize that the relative importance of delocalization and polar effects depends on the nature of the charge that develops in the TS or the intermediate. The delocalization effects of most substituents are in opposite directions, depending on whether a negative or a positive charge is involved, but there are exceptions. Phenyl and vinyl groups can stabilize either negative or positive charges by delocalization. In Section 3.6, we discuss *linear free-energy relationships*, which permit the quantitative description of substituent effects. At this point, however, we want to make a qualitative assessment. Scheme 3.1 lists a number of common substituent groups and indicates whether the group is an ERG or an EWG substituent. The effects of substituents are shown separately for resonance and polar interactions. In the discussions of substituent effects in future chapters, we frequently make reference to the electronic effects of ERG and EWG substituents.

We can quickly note some of the general features of the various types of substituents. Alkyl groups are electron releasing by virtue of σ delocalization (hyperconjugation) and small polar effects. The π and π^* orbitals of vinyl, phenyl, and ethynyl groups allow them to delocalize both positive and negative charges. Because of the greater electronegativity of sp^2 and especially sp carbon, relative to sp^3 carbon, the unsaturated groups are weakly electron attracting from the polar perspective. (See p. 12–13 to review carbon electronegativity trends.) Oxygen and nitrogen substituents having unshared electron pairs are strong electron donors by resonance. Alkoxy, acyloxy, amino, and acylamido are common examples of this kind of group. On the other hand, because of the higher electronegativity of oxygen and nitrogen relative to carbon, they are EWGs through polar interactions. This is especially true of the acyloxy and acylamido groups because of the dipole associated with the carbonyl group. All the various carbonyl functional groups are EWG through both resonance and polar contributions. The C=O bond dipole and the higher electronegativity of the carbonyl carbon both contribute to the latter effect.

The halogens are an interesting group. They act as electron donors by resonance involving the unshared pairs, but this is opposed by a polar effect resulting from their

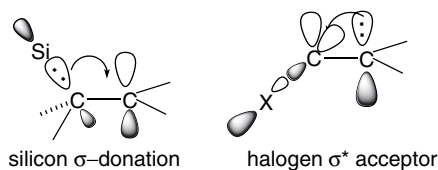
Scheme 3.1. Classification of Substituent Groups

Substituent	Resonance	Polar
<u>Alkyl</u>		
CH ₃ , C ₂ H ₅ , (CH ₃) ₃ C, etc	ERG	ERG (small)
<u>Vinyl and aryl</u>		
CH ₂ =CH, C ₆ H ₅ , etc	ERG or EWG	EWG (small)
<u>Ethynyl</u>		
HC≡C, etc	ERG or EWG	EWG
<u>Alkoxy, Acyloxy, Amino, Acylamido</u>		
RO, RCO ₂ , R ₂ N, RCONH, etc	ERG	EWG
<u>Carbonyl</u>		
HC=O, RC=O, ROC=O, R ₂ NC=O, etc.	EWG	EWG
<u>Halogens</u>		
F, Cl, Br, I	ERG	EWG
<u>Polyhaloalkyl</u>		
CF ₃ , CCl ₃ , etc.	EWG	EWG
<u>Other Nitrogen Groups</u>		
CN, NO ₂ , R ₃ N ⁺ , etc.	EWG	EWG
<u>Sulfur Groups</u>		
RS	ERG	EWG
RSO	ERG	EWG
RSO ₂	EWG	EWG
<u>Silyl Groups</u>		
R ₃ Si	ERG	ERG

SECTION 3.4

*Electronic Substituent
Effects on Reaction
Intermediates*

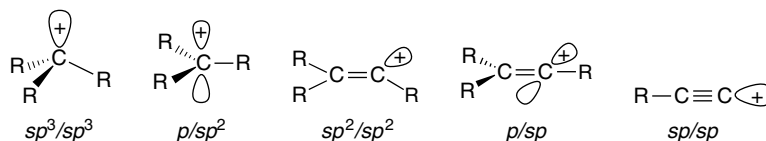
higher electronegativity. Moreover, the resonance and polar effects both weaken going down the periodic table. Resonance weakens because of longer bonds and poorer orbital overlap with carbon, whereas the polar effect decreases as the electronegativity diminishes. As a result, the halogens often exhibit unusual trends resulting from a changing balance between the resonance and polar effects. Halogen substituent effects are also affected by polarizability, which increases from fluorine to iodine. When halogen is placed on a carbon, as in trifluoromethyl or trichloromethyl, the groups are EWG by both polar and resonance mechanisms. The resonance component is associated with σ^* orbitals. The sulfur substituents RS, RSO, and RSO₂ show a shift from being resonance donors to strong polar acceptors, as the sulfur unshared pairs are involved in bonding to oxygen. Trialkylsilyl groups are slightly better ERGs than alkyl, since the silicon is less electronegative than carbon. Trialkylsilyl groups are very good electron donors by hyperconjugation.



There are many types of reaction intermediates that are involved in organic reactions. In this section we consider substituent effects on four important examples—carbocations, carbanions, radicals, and carbonyl addition (tetrahedral) intermediates—which illustrate how substituent effects can affect reactivity. Carbocation and carbanions are intermediates with positive and negative charge, respectively, and we will see that they have essentially opposite responses to most substituent groups. We also discuss substituent effects on neutral radical intermediates, where we might not, at first glance, expect to see strong electronic effects, since there is no net charge on the intermediate. The fourth case to be considered is the important class of carbonyl addition reactions, where substituent effects in the *reactant* often have the dominant effect on reaction rates.

3.4.1. Carbocations

Carbocations have a vacant orbital that bears a positive charge. Within the standard hybridization framework, there are five possible hybridization types if all the electrons are paired.

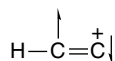


The approximate relative energies of these structures are illustrated in Figure 3.18. For trivalent carbon, the preferred hybridization is for the positive charge to be located in an unhybridized *p* orbital. Similarly, the *p/sp* hybridization is preferred for alkenyl carbocations. These hybridizations place the charge in a less electronegative *p*

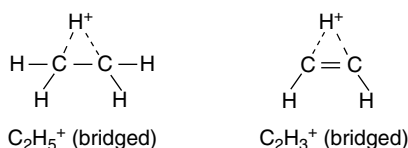
	MP4(SDQ)/6-31G**	MP2/6-31G*
HC≡C ⁺		+ 55.3
CH ₃ ⁺	-----0.0 Reference-----	
C ₆ H ₅ ⁺		-26.5
C ₂ H ₃ ⁺ (bridged)		-25.6
CH ₃ CH ₂ ⁺ (bridged)	-33.8	-40.8
CH ₃ CH ₂ ⁺ (open)	-39.0	-34.4
CH ₂ =C ⁺ CH ₃	-42.9	-46.5
CH ₂ =CHCH ₂ ⁺	-54.5	-60.0
(CH ₃) ₂ C ⁺ H	-58.5	-58.9
C ₆ H ₅ CH ₂ ⁺		-74.5
(CH ₃) ₃ C ⁺		-75.0

Fig. 3.18. Gas phase carbocation stabilities relative to methyl cations in kcal/mol. Data from Y. Apeloig and T. Müller, in *Dicoordinated Carbocations*, Z. Rapoport and P. J. Stang, eds., John Wiley & Sons, New York, 1997, Chap.2.

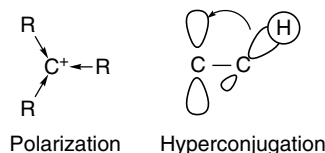
orbital. The sp^3/sp^3 and sp^2/sp^2 arrangements are not energy minima, but lie at least 20–30 kcal above the p/sp^2 and p/sp arrangements.⁶⁵ The very high relative energy of terminal ethynyl carbocations reflects the fact that the positive charge is associated with a more electronegative sp orbital if the triple bond is retained. Various MO computations indicate that the ethynyl cation adopts an alternative electronic configuration which places the positive charge in a π orbital, but the cation is nevertheless very unstable.⁶⁶



Certain carbocations, especially in the gas phase, appear to be *bridged*. This is true for ethyl and vinyl cations. More will be said about bridging in Section 4.4.



The carbocation stability order $CH_3 < pri < sec < tert$ is due to the electron-releasing effect of alkyl substituents. The electron release is a combination of a polar effect that is due to the greater electronegativity of the sp^2 carbon and a hyperconjugative effect through which the electrons in σ C–H and C–C bonds of the alkyl group are delocalized to the empty p orbital. The delocalization has a stereoelectronic aspect, since alignment of a C–H (or C–C) bond with the empty p orbital maximizes electron delocalization. Gas phase experimental⁶⁷ and computational⁶⁸ data (Figure 3.18) indicate that the stabilization energies are as follows (relative to methyl in kcal/mol): CH_3^+ (0, 0); $CH_3CH_2^+$ (40, 41), $(CH_3)_2CH^+$ (60, 59); $(CH_3)_3C^+$ (85, 75).

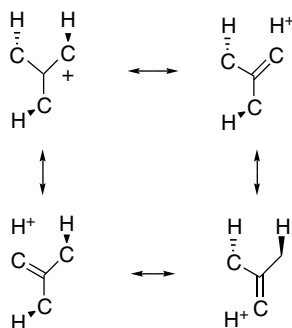


⁶⁵ Y. Apeloig and T. Müller in *Dicoordinated Carbocations*, Z. Rappoport and P. J. Stang, eds., John Wiley & Sons, New York, 1997, Chap. 2; J. Abboud, I. Alkorta, J. Z. Davalos, P. Muller, and E. Quintanilla, *Adv. Phys. Org. Chem.*, **37**, 57 (2002).

⁶⁶ L. A. Curtiss and J. A. Pople, *J. Chem. Phys.*, **91**, 2420 (1989); W. Koch and G. Frenking, *J. Chem. Phys.*, **93**, 8021 (1990); K. Hashimoto, S. Iwata, and Y. Osamura, *Phys. Chem. Lett.*, **174**, 649 (1990).

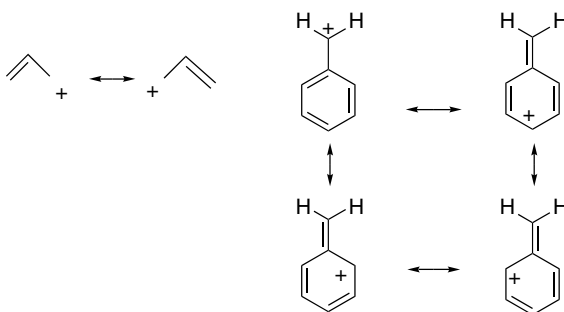
⁶⁷ D. H. Aue, in *Dicoordinated Carbocations*, Z. Rappoport and P. J. Stang, eds., John Wiley & Sons, New York, 1997, Chap. 3; D. H. Aue and M. T. Bowers, in *Gas Phase Ion Chemistry*, M. T. Bowers, ed., Academic Press, New York, 1979.

⁶⁸ Y. Apeloig and T. Müller, in *Dicoordinated Carbocations*, Z. Rappoport and P. J. Stang, eds., John Wiley & Sons, New York, 1997, Chap. 2.



Resonance Representation of Hyperconjugation

Carbocations that are adjacent to π bonds, as in allylic and benzylic carbocations, are strongly stabilized by delocalization. The stabilization in the gas phase is about 60 kcal/mol for the allyl cation and 75 kcal/mol for benzyl ions, relative to the methyl cation.⁶⁷



Resonance representation of allylic and benzylic stabilization

Total resonance stabilization has been calculated at the MP2/6-31G* level for a number of conjugated ions, as shown in Table 3.9. One general trend seen in this data is a decrease of the effect of successive phenyl rings in the benzyl, diphenylmethyl, and triphenylmethylium series. Two factors are involved. The effect of resonance stabilization is decreased because the successive rings must be twisted from planarity. This factor and related steric repulsions attenuate the effect of each successive phenyl group relative to methyl (see Column B). In the allyl series a 1-phenyl substituent adds 39.4 kcal of stabilization, while a 2-phenyl group adds only 11.4.⁶⁹

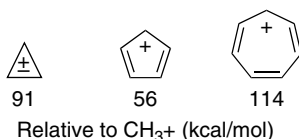
Table 3.9. Stabilization Energy in kcal/mol for Delocalized Carbocations

Carbocation	Resonance stabilization	Stabilization relative to CH_3^+
$\text{C}_6\text{H}_5\text{CH}_2^+$	76.4	75.4
$\text{CH}_2=\text{CHCH}_2^+$	53.2	
$(\text{C}_6\text{H}_5)_2\text{CH}^+$	102.7	91.6
$(\text{C}_6\text{H}_5)_3\text{C}^+$	124.8	102.2
$\text{C}_6\text{H}_5\text{C}^+\text{HCH}=\text{CH}_2$	92.6	
$\text{CH}_2=\text{C}(\text{C}_6\text{H}_5)\text{CH}_2^+$	64.6	

a. B. Reindl, T. Clark and P. v. P. Schleyer, *J. Phys. Chem. A*, **102**, 8953 (1998).

⁶⁹ B. Reindl, T. Clark, and P. v. R. Schleyer, *J. Phys. Chem. A*, **102**, 8953 (1998).

When the vacant p orbital is part of a completely conjugated cyclic system, there can be further stabilization resulting from aromaticity. (See Section 8.3 for further discussion.) The cyclopropenylum ion and the cycloheptatrienylium ion fit into this category. When cyclic conjugation is antiaromatic, as in the cyclopentadienylium ion, there is net stabilization relative to a methyl cation, but significantly less than for the aromatic analogs.⁷⁰



Carbocation stability in the gas phase can be measured by mass spectrometry and reported as *hydride affinity*, which is the enthalpy of the reaction:

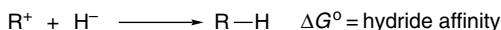


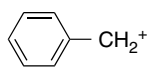

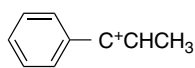

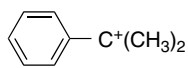


Table 3.10 gives values for the hydride affinity for some carbocations. There is good agreement with the theoretical results shown in Figure 3.18 and the data in Table 3.10.

Substituents such as oxygen and nitrogen that have nonbonding electrons are very strongly stabilizing toward carbocations. This is true both for ether-type oxygen and carbonyl-type oxygen (in acylium ions). Even fluorine and the other halogens are

Table 3.10. Hydride Affinity of Some Carbocations

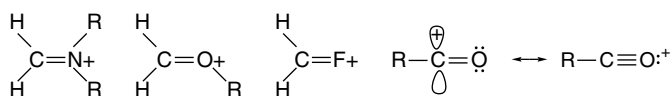
Hydride affinity (kcal/mol)			
	Gas ^a		Gas ^a
CH ₃	314	CH ₂ =CHCH ₂ ⁺	256
CH ₃ CH ₂ ⁺ (bridged)	270	CH ₂ =CHCC ⁺ HCH ₃	239
(CH ₃) ₂ CH ⁺	252	CH ₂ =CHC ⁺ (CH ₃) ₂	230
(CH ₃) ₃ C ⁺	237	CH ₃ CH=CHC ⁺ HCH ₃	228
CH ₂ =CH ⁺ (bridged)	288		284
	223 ^b		239
	258 ^b		225
	200 ^b		220 ^b

a. From D. H. Aue in *Dicordinate Carbocations*, Z. Rappoport and P. J. Stand, eds., John Wiley & Sons, New York, 1997, Chap. 3.

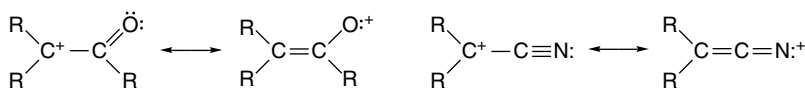
b. From D. H. Aue and M. T. Bowers, in *Gas Phase Ion Chemistry*, M. T. Bowers, ed., Academic Press, New York, 1979.

⁷⁰. Y. Mo, H. Jiao, Z. Lin, and P. v. R. Schleyer, *Chem. Phys. Lett.*, **289**, 383 (1998).

stabilizing by delocalization (but we discuss the opposing polar effect of the halogens below).



The stabilizing effect of delocalization can be seen even with certain functional groups that are normally considered to be electron withdrawing. For example, computations indicate that cyano and carbonyl groups have a stabilizing resonance effect. This is opposed by a polar effect, so the net effect is destabilizing, but the resonance component is stabilizing.



Resonance stabilization of carbocations by electron pair donation

Table 3.11 shows some gas phase stabilization energies computed by various methods. Columns A and B refer to stabilization of substituted methyl (methylium) carbocations, whereas columns C and D are referenced to ethylium ions. Because these values refer to the gas phase, where there is no solvation, the absolute stabilization energies are substantially larger than those found in solution studies. Nevertheless, the results provide a good indication of the relative effect of the various substituents on carbocation stability. Note that of all the substituents included, only NO_2 is strongly destabilizing. The data for F, Cl, CN, and $\text{CH}=\text{O}$ indicate small stabilization, reflecting the compensating polar (destabilizing) and delocalization (stabilizing) effects mentioned earlier.

The most wide-ranging and internally consistent computational comparison of substituent effects on carbocation was reported by a group working in The

Table 3.11. Calculated Substituent Stabilization on Carbocations (in kcal/mol)

Substituent	CH_3^+		CH_3CH_2^+	
	PM3 ^a	MP2/6-31G ^{**b}	MP2/6-311+G(<i>d,p</i>) ^c	B3LYP/6-311+G(<i>d,p</i>) ^c
NH_2	80.2			
CH_3O	57.6			
OH	51.4			
Ph	56.3			
$\text{CH}_2=\text{CH}$	43.3	66.1	30.9	37.3
CH_3	29.0	41.5	17.1	23.4
F	5.5		6.0	7.1
Cl			9.7	10.6
CN	5.0	4.3		
$\text{CH}=\text{O}$	1.7	0.2		
NO_2	-30.8	-22.3		

a. A. M. El-Nahas and T. Clark, *J. Org.Chem.*, **60**, 8023 (1995).

b. X. Creary, X.Y. Wang, and Z. Jiang, *J. Am. Chem. Soc.*, **117**, 3044 (1995).

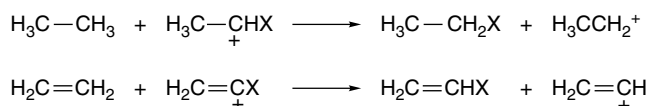
c. K. van Alem, E. J. R. Sudholter, and H. Zuilhof, *J. Phys. Chem. A*, **102**, 10860 (1998).

Table 3.12. Computed Substituent (De)Stabilization of Carbocation (in kcal/mol)^a

X	Ethyl	Vinyl	X	Ethyl	Vinyl
H	0.00	0.00	C≡N	-16.02	-11.71
CH ₃	18.63	25.89	CH=O	-10.25	-4.51
CH ₂ OH	15.30	21.69	CO ₂ H	-8.41	-5.92
CH ₂ CN	-2.10	4.76	H ₂ N	64.96	53.69
CH ₂ Cl	5.59	12.90	HO	37.43	25.92
CH ₂ CF ₃	3.62	9.63	O ₂ N	-23.09	-25.44
CH ₂ F	4.98	10.89	F	6.95	-9.25
CF ₃	-23.56	-16.41	Cl	9.83	11.17
CH ₂ =CH	31.98	25.64	Br	9.52	12.70
HC≡C	18.17	25.64	I	13.32	20.53
C ₆ H ₅	36.77	54.10			
c-C ₃ H ₅	42.97	47.06			

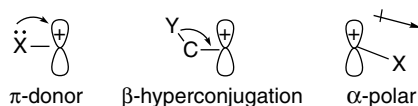
a. K. van Alem, G. Lodder, and H. Zuilhof, *J. Phys. Chem.*, **106**, 10681 (2002).

Netherlands.⁷¹ This study compared MP2/6-311++G(*d,p*), CBS-Q, and B3LYP/6-311+G(*d,p*) calculations and found that the CBS-Q method gave the best correlation with experimental data. There was also good correlation with MP2 and B3LYP results, which could be used to obtain “CBS-Q-like” results when the CBS-Q method was not applicable. Table 3.12 gives some of the computed stabilization (+) and destabilization (−) relative to ethyl and vinyl cations found using isodesmic reactions:



The results show substantial destabilization for CF₃, CN, CH=O, CO₂H, and NO₂ groups.

The relative stability, charge distribution, and bond orders obtained by the calculation identified three main factors in carbocation stabilization as π -donation, β -hyperconjugation, and the α -polar effects.



The π -donor and β -hyperconjugation effects are present for both alkyl and vinyl carbocations. The vinyl carbocations exhibit somewhat larger stabilizations because they are inherently less stable. The vinyl cations also appear to be more sensitive to the α -polar effect. Note that the F, OH, and NH₂ substituents are less stabilizing of vinyl cations than of alkyl cations. This is believed to be due to the greater sensitivity to the polar effect of the more electronegative *sp* carbon in the vinyl cations. The NPA and bond order characterizations of the carbocations are shown in Table 3.13. The values give the charge associated with the cationic carbon and the bond order between the cationic carbon and the substituent X.

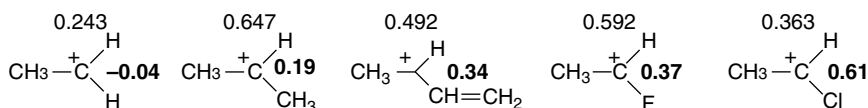
⁷¹ K. van Alem, G. Lodder, and H. Zuilhof, *J. Phys. Chem. A.*, **106**, 10681 (2002).

Table 3.13. NPA and Bond Order Characterizations of Substituted Carbocations

X	C(+)		C ⁺ -X Bond Order	
	Alkyl	Vinyl	Alkyl	Vinyl
CH ₃	0.647	0.585	0.19	0.20
CH ₂ OH	0.702	0.568	0.15	0.17
CH ₂ CN	0.633	0.598	0.15	0.18
CH ₂ Cl	0.719	0.585	0.18	0.16
CH ₂ F	0.659	0.577	0.14	0.15
CH ₂ CF ₃	0.612	0.601	0.13	0.18
CF ₃	0.666	0.618	-0.07	-0.06
CH ₂ =CH	0.492	0.440	0.34	0.27
HC≡C	0.542	0.704	0.28	0.29
C ₆ H ₅	0.420	0.383	0.40	0.29
<i>c</i> -C ₃ H ₅	0.558	0.525	0.46	0.42
C≡N	0.602	0.572	0.13	0.15
HC=O	0.664	0.656	0.02	-0.03
HO ₂ C	0.650	0.587	-0.02	-0.02
H ₂ N	0.531	0.394	0.55	0.47
HO	0.242	0.125	0.76	0.67
O ₂ N	0.499	0.424	0.02	0.04
F	0.592	0.524	0.37	0.39
Cl	0.363	0.274	0.61	0.60
Br	0.284	0.205	0.67	0.65
I	0.193	0.123	0.74	0.68

a. K. van Alem, G. Lodder, and H. Zuilhof, *J. Phys. Chem. A*, **106**, 10681 (2002).

Except for π -donor substituents, most of the positive charge resides on the cationic carbon. The strongest effect is seen for the halogens, where there is a sharp drop in the positive charge in the order $F > Cl > Br > I$. Note from the NPA charge at the cationic carbon that F is more effective than CH₃ in delocalizing the positive charge. However, the net stabilization is much less because the polar effect of the σ C–F bond is strongly destabilizing.⁷² The resonance effect is also indicated by increased bond order to the substituent (shown in bold).



Charge on trivalent carbon (upper) and bond order (bold) on carbocation

One feature of the charge distributions in carbocations that deserves attention is the greater positive charge calculated for the trigonal carbon in 2-propyl cation than for ethyl cation. This tendency for more substituted alkyl carbocations to be *more positive* has been found in other calculations⁷³ and is consistent with the relative ¹³C chemical shifts observed in NMR.⁷⁴ How does this relationship accord with the very strong *stabilizing* influence on alkyl groups on carbocations? Levy⁷⁵ has argued that

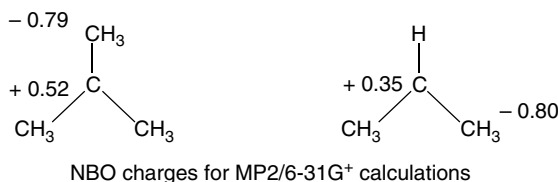
⁷². K. van Alem, E. J. R. Sudhölter, and H. Zuilhof, *J. Phys. Chem. A*, **102**, 10860 (1998).

⁷³. R. Hoffmann, *J. Chem. Phys.*, **40**, 2480 (1964).

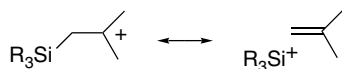
⁷⁴. G. A. Olah and A. M. White, *J. Am. Chem. Soc.*, **91**, 5801 (1969).

⁷⁵. J. B. Levy, *Struct. Chem.*, **10**, 121 (1999).

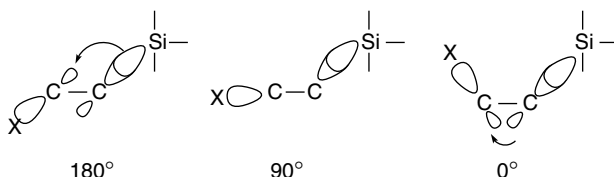
the alternating (+) and (−) charges found in tertiary cations provide the source of the stabilization. The hydrogens bear most of the positive charge according to NPA charge assignment.



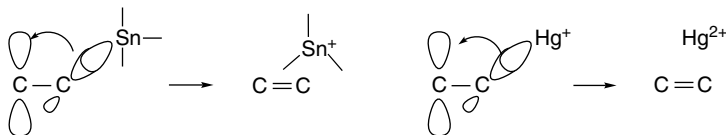
Silicon substitution β to a carbocation is very stabilizing by hyperconjugation.⁷⁶



This stabilization has been shown to be primarily a delocalization effect by demonstrating a strong dependence on the dihedral angle between the Si—C bond and the empty p orbital of the carbocation. Kinetic rate enhancements of about 1012, 0, and 104 were found for compounds with angles of 180°, 90°, and 0°, respectively. This is consistent with a hyperconjugation mechanism and with analyses of orbital overlap that show considerably stronger overlap for the *anti* (180°) than *syn* (0°) orientations.⁷⁷

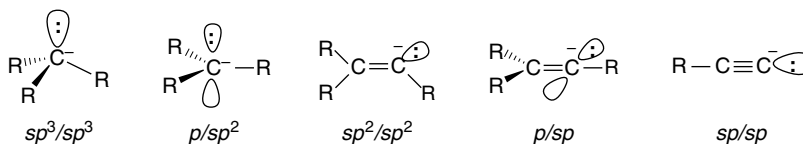


This β -stabilization is even stronger for less electronegative elements such as tin and mercury. In effect, the electron release is complete and elimination occurs. We discuss this kind of reaction further in Section 5.10.5.



3.4.2. Carbanions

Carbanions have negative charge on carbon and, as with carbocations, there are several conceivable hybridization schemes.



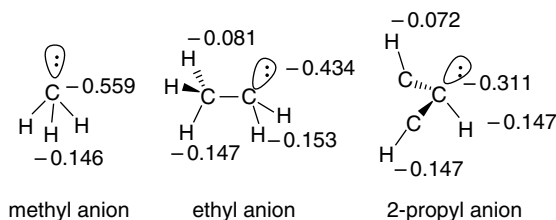
⁷⁶ J. B. Lambert, *Tetrahedron*, **46**, 2677 (1996); J. B. Lambert, Y. Zhao, R. W. Emblidge, L. A. Salvador, X. Liu, J. -H. So, and E. C. Chelius, *Acc. Chem. Res.*, **32**, 183 (1999).

⁷⁷ A. J. Green, Y. -I. Kuan, and J. M. White, *J. Org. Chem.*, **60**, 2734 (1995).

Because the nonbonding orbital is occupied, stability increases with s character, the converse of the situation for carbocations. The order of stability of carbanions is $sp^3 < sp^2 < sp$. The relative stability of gas phase carbanions can be assessed by the energy of their reaction with a proton, which is called *proton affinity*. The proton affinities of the prototypical hydrocarbons methane, ethene, and ethyne have been calculated at the MP4/6-31+G* level.⁷⁸ The order is consistent with the electronegativity trends discussed in Section 1.1.5, and the larger gap between sp and sp^2 , as compared to sp^2 and sp^3 , is also evident. The relative acidity of the hydrogen in terminal alkynes is one of the most characteristic features of this group of compounds.

Proton affinity (kcal/mol)		
$R^- + H^+ \longrightarrow R-H$		
CH_4	$H_2C=CH_2$	$HC\equiv CH$
419.4	408.7	375.1

The order of gas phase carbanion stability has been calculated as $Et < Me \sim iso-Pr < tert-Bu$ by both MP2/6-31 + G(d,p) and B3LYP/6-31 + G(d,p) calculations.⁷⁹ Experimental values in the same order have been recorded.⁸⁰ The *pri* < *sec* < *tert* order reflects the ability of the larger groups to disperse the negative charge (polarizability). The $Et < Me$ order indicates that electron donation by CH_3 (relative to H) slightly destabilizes the ethyl carbanion. However, a larger *tert*-butyl substituent (in the neopentyl anion) has a net stabilizing effect that is evidently due to polarizability. Note that the effect of substitution is *very much smaller* than for carbocations. The range between primary and tertiary carbanions is only about 10 kcal/mol, compared to about 75 kcal/mol for carbocations. The alkyl anions are calculated to be pyramidal, in agreement with the sp^3 hybridization model. The bond angles at the trivalent carbon are as follows: CH_3^- : 109.4°; $CH_3CH_2^-$: 111.0°; $(CH_3)_2CH^-$: 109.1°, and $(CH_3)_3C^-$: 109.6°.⁸¹ AIM charges were also calculated (B3LYP/6-311 + G**), as shown below, and indicate some σ -delocalization to the β -hydrogens. Note in particular that in the ethyl and 2-propyl anions the *anti* hydrogens are more negative than the *gauche*. Note also the considerable reduction in the charge at carbon as the anion becomes larger. These trends are in accord with dispersal of the negative charge by both hyperconjugation and polarization. Table 3.14 compares proton affinities calculated by several methods with experimental values.



⁷⁸ W. H. Saunders, Jr., and J. E. Van Verth, *J. Org. Chem.*, **60**, 3452 (1995).

⁷⁹ R. R. Sauers, *Tetrahedron*, **55**, 10013 (1999).

⁸⁰ C. H. DePuy, S. Gronert, S. E. Barlow, V. M. Bierbaum, and R. Damrauer, *J. Am. Chem. Soc.*, **111**, 1968 (1989).

⁸¹ P. Burk and K. Sillar, *Theochem*, **535**, 49 (2001).

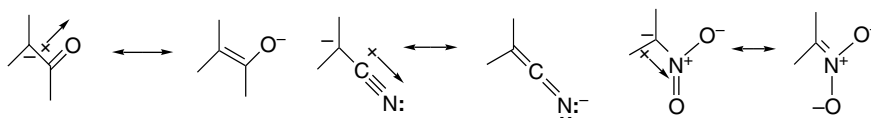
Table 3.14. Computational and Experimental Proton Affinities for Small Hydrocarbons (in kcal/mol)

Group	MP2/6-31+G(d,p) ^a	B3LYP/6-311G(3df,2dp) ^a	G2 ^b	Experimental ^c
CH ₃ ⁻	419.0	414.5	418.4	415–421.5
CH ₃ CH ₂ ⁻	421.8	417.0	420.6	420.1
(CH ₃) ₂ CH ⁻	419.6	413.4	418.3	419.4
(CH ₃) ₃ C ⁻	412.1	406.9	412.2	413.1
c-(CH ₂) ₂ CH ⁻	415.5	411.3		409–413.5

a. R. R. Sauers, *Tetrahedron*, **55**, 10013 (1999).b. P. Burk and K. Sillar, *Theochem*, **535**, 49 (2001).

c. Range of values includes quoted error ranges.

Electron-withdrawing groups such as carbonyl, cyano, and nitro strongly stabilize carbanions as the result of complementary resonance and polar effects. Table 3.15 gives some computed stabilization energies for various substituent groups.



The stabilization by substituents such as F and OH is presumably due to polar effects. Note that there is considerable discrepancy between the semiempirical and ab initio results, as the former indicate much greater substituent stabilization for the second-row elements C through F. The large stabilizing effect for BH₂ is due to the capacity of the –BH₂ group to accept two electrons. The effect of the heavier substituents, Cl through SiH₃, is primarily due to polarizability. Very large stabilizations owing to delocalization are seen for the conjugated substituents CH₂=CH through NO₂.

Third- and fourth-row substituents such as sulfenyl, sulfinyl, sulfonyl, phosphinyl, and selenenyl stabilize carbanions. Because these substituents have tetrahedral

Table 3.15. Calculated Stabilization Energies for Methyl Anions (in kcal/mol)

Substituent	AM1 ^a	AM1 _(H₂O) ^a	PM ^a	PM _(H₂O) ^a	MP2/6-31G ^{ab}	MP4SDQ/6-31G ^{ab}	QCISD(T)/6-31G ^{ab}
F	19.4	14.4	24.6	21.0	9.09	10.52	10.23
OH	15.9	12.0	19.4	16.4	5.15	5.58	5.70
NH ₂	20.1	13.3	20.9	15.1	–0.67	–0.74	0.46
CH ₃	14.5	4.6	14.7	5.7	3.14	3.32	2.99
BH ₂					57.34	56.83	57.90
Cl					18.13	19.48	19.36
SH					20.98	20.45	20.53
PH ₂					23.45	22.37	22.25
SiH ₃					25.27	24.78	24.79
CH=CH ₂	45.5	29.4	33.0	31.4			
CH=O	62.7		60.3				
CN	55.0	41.2	59.4	49.3			
NO ₂	85.8	69.7	91.9	72.5			
Li					8.95	17.83	24.39
Na					5.04	16.99	21.92

a. M. El-Nahas, *J. Chem. Res. (Synop.)*, 310 (1996).b. A. M. El-Nahas and P. v. R. Schleyer, *J. Comput. Chem.*, **15**, 596 (1994).

hybridization, the question arises as to whether the stabilization is through delocalization, polar, or polarization effects. The α substituents increase acidity in the order $\text{Se} > \text{S} > \text{O}$ and $\text{Br} > \text{Cl} > \text{F}$, which indicates that some factor apart from electronegativity (bond polarity) must contribute to the stabilization. The stabilization has been described both in terms of polarization and d orbital participation for the larger elements. The latter effect, as expressed in resonance terminology, implies shortening of the C–X bond. G2 calculations show very slight shortening for the C–PH₂ and C–SH bonds, but the halogens do not show such a trend.⁸² Polarization appears to be the main mechanism for carbanion stabilization by the heavier elements.⁸³

Another computational approach to assessing carbanion stabilization by substituents entails calculation of proton affinity. Table 3.16 gives the results of G2 and MP4/6-31G* computations. The energy given is the energy required to remove a proton from the methyl group. The strong stabilization of the π -electron acceptors, such as BH₂, CH=O, NO₂, and CN, is evident. The second-row elements are in the order of electronegativity $\text{F} > \text{OH} > \text{NH}_2$, but the effects are comparatively small. The stabilization by third- and fourth-row elements (S, P, Se) are reproduced, and the halogen order, $\text{F} < \text{Cl} < \text{Br}$, also suggests that polarization is more important than dipolar stabilization.

These computational studies provide a description of carbanion stabilization effects that is consistent with that developed from a range of experimental observations. The strongest effects come from conjugating EWG substituents that can delocalize the negative charge. Carbon atom hybridization is also a very strong effect. The effect of saturated oxygen and nitrogen substituents is relatively small and seems to be $\text{O} > \text{N}$, suggesting a polar effect. This may be opposed by electron-electron repulsion arising from the unshared electrons on nitrogen and oxygen.

Table 3.16. Gas Phase Proton Affinity of Substituted Methanes (in kcal/mol)

Compound	G2 ^a	MP4/6-31G ^{ab}
CH ₃ NH ₂	418.8	
CH ₃ OH	414.6	417.7 ^b
CH ₃ OCH ₃	412.8	
CH ₃ PH ₂	393.9	
CH ₃ SH	397.6	403.1 ^b
CH ₃ SeH		399.3 ^b
CH ₃ F	410.4	412.6 ^b
CH ₃ Cl	398.2	404.5 ^b
CH ₃ Br	393.5	400.3 ^b
CH ₃ BH ₂	363.0	
CH ₃ CH=O	368.1	367.1 ^c
CH ₃ CH=CH ₂		392.5 ^c
CH ₃ NO ₂	358.4	
CH ₃ CN	375.0	375.9 ^c

a. P. M. Mayer and L. Radom, *J. Phys. Chem. A*, **102**, 4918 (1998).

b. J. E. Van Verth and W. H. Saunders, Jr., *J. Org. Chem.*, **62**, 5743 (1997).

c. W. H. Saunders, Jr., and J. E. Van Verth, *J. Org. Chem.*, **60**, 3452 (1995).

⁸². P. M. Mayer and L. A. Radom, *J. Phys. Chem. A*, **102**, 4918 (1998).

⁸³. P. Speers, K. E. Laidig, and A. Streitwieser, *J. Am. Chem. Soc.*, **116**, 9257 (1994).

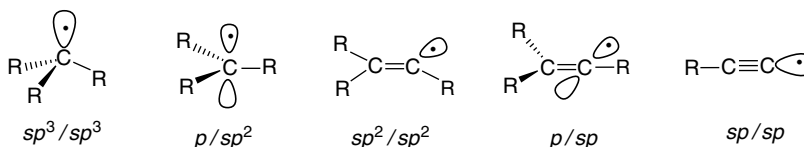
There is also a good deal of information available on carbanion stability in solution.⁸⁴ These data are derived from equilibrium measurements analogous to acid dissociation constants, in which the extent of deprotonation of hydrocarbons by strong base is determined:



Only a few hydrocarbon derivatives can be directly measured in aqueous solution, but extensive studies have been done in other solvents, in particular DMSO. We consider this solution data in Chapter 6.

3.4.3. Radical Intermediates

Carbon radicals have an unpaired electron in a nonbonding orbital. The possible hybridization schemes are shown below.



The methyl radical is close to planarity.⁸⁵ Experimental⁸⁶ and computational⁸⁷ results indicate that simple alkyl radicals are shallow pyramids with low barriers for inversion, which is consistent with p/sp^2 hybridization. The ethenyl radical is bent with a C–C–H bond angle of 137° .⁸⁸ High-level MO calculations arrive at a similar structure.⁸⁹ This geometry indicates sp^2/sp^2 hybridization. The alkenyl radicals can readily invert through the linear p/sp radical as a transition structure.⁹⁰ A major structural effect in alkyl (beyond methyl) and alkenyl radicals is a marked weakening of the β -C–H bonds, which occurs by interaction of the β -C–H and the SOMO (singly occupied molecular orbital). According to both computational (CBS-4) and thermodynamic cycles, the strength of the β -C–H bond is only 30–35 kcal/mol.⁹¹ This leads to one of the characteristic bimolecular reactions of alkyl radicals—disproportionation to an alkane and an alkene. Similar values pertain to β -C–H bonds in vinyl radicals.



⁸⁴. E. Buncl and J. M. Dust, *Carbanion Chemistry*, Oxford University Press, Oxford, 2003.

⁸⁵. M. Karplus and G. K. Fraenkel, *J. Chem. Phys.*, **35**, 1312 (1961); L. Andrews and G. C. Pimentel, *J. Chem. Phys.*, **47**, 3637 (1967); E. Hirota, *J. Phys. Chem.*, **87**, 3375 (1983).

⁸⁶. M. Karplus and G. K. Fraenkel, *J. Chem. Phys.*, **35**, 1312 (1961); L. Andrews and G. C. Pimentel, *J. Chem. Phys.*, **47**, 3637 (1967); E. Hirota, *J. Phys. Chem.*, **87**, 3375 (1983); T. J. Sears, P. M. Johnson, P. Jin, and S. Oatis, *J. Phys. Chem.*, **104**, 781 (1996).

⁸⁷. F. M. Bickelhaupt, T. Ziegler, and P. v. R. Schleyer, *Organometallics*, **15**, 1477 (1996); M. N. Paddon-Row and K. N. Houk, *J. Phys. Chem.*, **89**, 3771 (1985); J. Pacansky, W. Koch, and M. D. Miller, *J. Am. Chem. Soc.*, **113**, 317 (1991); H. H. Suter and T. K. Ha, *Chem. Phys.*, **154**, 227 (1991); A. L. L. East and P. R. Bunker, *Chem. Phys. Lett.*, **282**, 49 (1998).

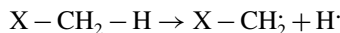
⁸⁸. J. H. Wang, H. -C. Chang, and Y. -T. Chen, *Chem. Phys.*, **206**, 43 (1996).

⁸⁹. L. A. Curtiss and J. A. Pople, *J. Chem. Phys.*, **88**, 7405 (1988); K. A. Peterson and T. H. Dunning, *J. Chem. Phys.*, **106**, 4119 (1997).

⁹⁰. P. R. Jenkins, M. C. R. Symons, S. E. Booth, and C. J. Swain, *Tetrahedron Lett.*, **33**, 3543 (1992).

⁹¹. X. -M. Zhang, *J. Org. Chem.*, **63**, 1872 (1998).

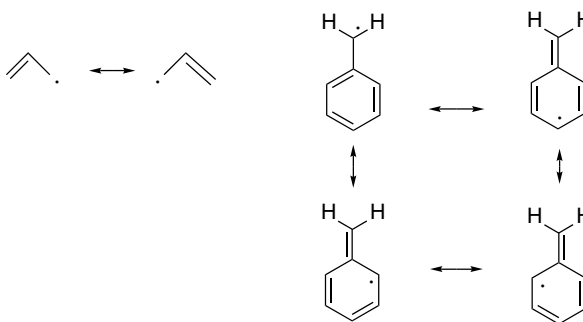
A good place to begin discussion of substituent effects on radicals is by considering the most common measure of radical stability. Radical stabilization is often defined by comparing C–H bond dissociation energies (BDE). For substituted methanes, the energy of the reaction should reflect any stabilizing features in the radical $X-CH_2\cdot$.



The BDEs are usually tabulated as the enthalpy change for the reaction at 298 K. The values can be determined experimentally⁹² or calculated theoretically. Table 3.2 B (p. 258) gives some C–H BDE for important C–H bonds. The BDEs become smaller in the order $CH_3 > pri > sec > tert$. The relatively low enthalpies of the dissociation for forming allyl and benzyl radicals by removal of hydrogen from propene and toluene, respectively, is due to the stabilization of these radicals by delocalization. On the other hand the C–H bond to sp^2 (ethene, benzene) and sp (ethyne) carbon are substantially stronger than bonds to sp^3 carbon. The BDEs correlate with the ease of formation of the corresponding radicals.⁹³ The reactivity of C–H groups toward radicals that abstract hydrogen is $pri < sec < tert$. Vinyl and phenyl substituents at a reaction site weaken the C–H bond and enhance reactivity. On the other hand, hydrogen abstraction from an sp^2 (vinyl or aryl) C–H bond or from a sp carbon in a terminal alkyne is difficult because of the increased strength of the corresponding C–H bonds.

The trend of reactivity $tert > sec > pri$ is consistently observed in various hydrogen atom abstraction reactions, but the range of reactivity is determined by the nature of the reacting radical. The relative reactivity of *pri*, *sec*, and *tert* positions toward hydrogen abstraction by methyl radicals is 1:4.8:61.⁹⁴ An allylic or benzylic hydrogen is more reactive toward a methyl radical by a factor of about 9, compared to an unsubstituted C–H. The relative reactivity toward the *t*-butoxy radical is *pri*: 1, *sec*: 10, *tert*: 50.⁹⁵ In the gas phase, the bromine atom is much more selective, with relative reactivities of *pri*: 1, *sec*: 250, *tert*: 6300.⁹⁶ Data for other types of radicals have been obtained and tabulated.⁹⁶

The stabilizing effects of vinyl groups (in allylic radicals) and phenyl groups (in benzyl radicals) are large and can be described in resonance terminology.



⁹² J. Berkowitz, G. B. Ellison, and D. Gutman, *J. Phys. Chem.*, **98**, 2744 (1994).

⁹³ J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966).

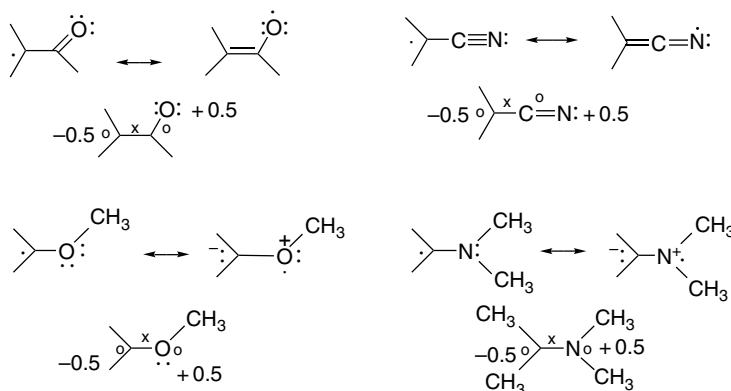
⁹⁴ W. A. Pryor, D. L. Fuller, and J. P. Stanley, *J. Am. Chem. Soc.*, **94**, 1632 (1972).

⁹⁵ C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, **82**, 6108 (1960).

⁹⁶ A. F. Trotman-Dickenson, *Adv. Free Radical Chem.*, **1**, 1 (1965).

For the vinyl substituent, the stabilization can be expressed in terms of simple Hückel MO (HMO) theory. The interaction of a p orbital with an adjacent vinyl group creates the allyl radical. In HMO calculations, the resulting orbitals have energies of $\alpha + 1.4\beta$, α , and $\alpha - 1.4\beta$. Thus the interaction of the p orbital with both the π and π^* orbitals leaves it at the same energy level, but the π and π^* levels are transformed to ψ_1 and ψ_3 of the allyl radical. There is a net stabilization of 0.8β for the two electrons in the more stable ψ_1 orbital. One measure of the stabilization energy is the barrier to rotation at a terminal methylene group. A value of 16.8 kcal/mol has been calculated.⁹⁷ The experimental barrier is 15.7 kcal/mol. Another measure of the stabilization is the lowering of the C–H BDE for the allylic bond in propene, which indicates a stabilization of 13.4 kcal/mol.⁹⁸

For radicals, nearly all functional groups are stabilizing. Both EWGs such as carbonyl and cyano and ERGs such as methoxy and dimethylamino have a stabilizing effect on a radical intermediate at an adjacent carbon. The stabilizing role of functional groups can be expressed in resonance terms. Resonance structures depict these interactions as delocalization of the unpaired electron into the substituent group. For unsaturated substituents, the resonance is analogous to the allyl radical. For donor substituents, a dipolar structure is involved. Linnett structures with three-electron bonds are also descriptive of the effect of donor substituents, and imply a degree of charge separation.



The radical-stabilizing effect of both types of substituents also can be described in MO terms. In this case, the issue is how the unpaired electron in a p orbital interacts with the orbitals of the adjacent substituent, such as vinyl, carbonyl, or methoxy. Figure 3.19 presents a qualitative description of the situation. For unsaturated EWG substituents such as carbonyl, the orbitals are similar to an allyl system, but the energies are lower because of the lower energy of the π and π^* orbitals of the carbonyl group. In the case of an π -electron acceptor there is a lowering of both the ψ_1 orbital and the SOMO containing the unpaired electron, that is, the radical is stabilized. The radical also is more *electrophilic* because the SOMO is lowered in energy. For an electron donor substituent, the strongest interaction is between the unpaired electron in the p orbital and a nonbonding pair on the electron donor. This interaction results in lowering the energy of the orbital occupied by the electron pair, while raising the energy of the

⁹⁷. D. A. Hrovat and W. T. Borden, *J. Phys. Chem.*, **98**, 10460 (1994).

⁹⁸. W. R. Roth, F. Bauer, A. Beitat, T. Ebbrecht, and M. Wustefel, *Chem. Ber.*, **124**, 1453 (1991).

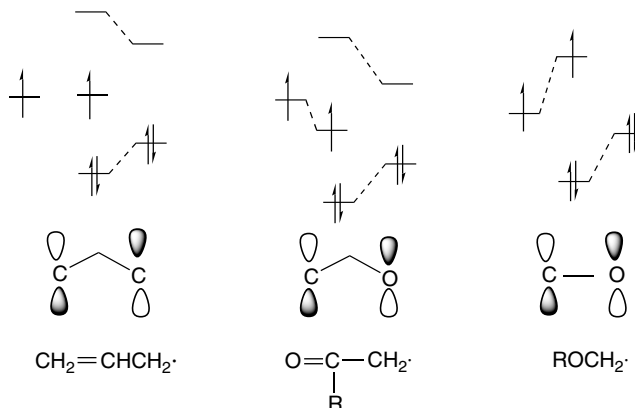


Fig. 3.19. PMO representation of p -orbital interactions with (a) $\text{C}=\text{C}$, (b) $\text{C}=\text{O}$, and (c) OR substituents. The form of the resulting SOMO is shown at the bottom.

orbital occupied by the single electron. The net effect is stabilizing, since there are two electrons in the stabilized orbital and only one in the destabilized one. The radical center is now more *nucleophilic* because the energy of the SOMO is raised.

Substituent effects on radicals can be expressed as *radical stabilization energies* (RSE). Table 3.17 gives some RSEs determined by one such approach developed by Leroy,^{99,100} which can be defined as the difference between the observed enthalpy of atomization ΔH_a and the sum of standard bond energies.

$$\text{RSE} = \Delta H_a - \Sigma \text{BE}$$

The ΔH_a can be obtained from thermodynamic data or calculated theoretically.¹⁰¹ These RSE values are generally consistent with chemical experience. For example, the low stability attributed to aryl and vinyl radicals, as opposed to the high stability of benzyl and allyl radicals, is consistent with their respective reactivities. The somewhat less familiar stability of aminoalkyl and acyl radicals is reproduced. The need for care is illustrated by the value for $\text{Cl}_3\text{C}\cdot$, which implies considerable *destabilization*. Chemical experience (see Section 11.4.2) shows that $\text{CCl}_3\cdot$ is a quite accessible species, although it appears in Table 3.17 as one of the most destabilized radicals. The C–H BDE for $\text{H}-\text{CCl}_3$ is intermediate between those for *pri* and *tert* C–H bonds. The apparent “destabilization” of $\text{CCl}_3\cdot$ is due to a “destabilization” that is also present in the reactant $\text{Cl}_3\text{C}-\text{H}$. Similarly, the acetyl radical is listed as destabilized, but it, too, is an accessible species. We return to this issue in Topic 11.1. Schemes for assignment of RSE that depend on the definition of standard bond energy terms are subject to the particular definitions that are used. These systems, however, are valuable in providing a basis for comparing substituent effects on a qualitative basis. These approaches can be

^{99.} G. Leroy, D. Peeters, and C. Wilante, *Theochem*, **5**, 217 (1982); G. Leroy, *Theochem*, **5**, 77 (1988).

^{100.} Other approaches to radical stabilization energies: C. Ruchardt and H. D. Beckhaus, *Top. Curr. Chem.*, **130**, 1 (1985); F. M. Welle, H.-D. Beckhaus, and C. Ruchardt, *J. Org. Chem.*, **62**, 552 (1997); F. G. Bordwell and X.-M. Zhang, *Acc. Chem. Res.*, **26**, 510 (1993); F. G. Bordwell, X.-M. Zhang, and R. Filler, *J. Org. Chem.*, **58**, 6067 (1993).

^{101.} J. Espinosa-Garcia and G. Leroy, *Recent Devel. Phys. Chem.*, **2**, 787 (1998).

Table 3.17. Thermochemical Stabilization Energies for Some Substituted Radicals (in kcal/mol)

	RSE ^a		RSE ^a
CH ₃ ·	-1.67	CH ₃ (OH)CH·	2.15
CH ₃ CH ₂ ·	2.11	(NC)FCH·	-2.79
NCCH ₂ ·	6.50	F ₂ CH·	-4.11
NH ₂ CH ₂ ·	3.92	(CH ₃) ₃ C·	4.35
CH ₃ NHCH ₂ ·	12.18	CH ₃ Ċ(CN) ₂	3.92
(CH ₃) ₂ NCH ₂ ·	14.72	CH ₃ Ċ(OH) ₂	0.15
HOCH ₂ ·	3.13	CH ₃ Ċ(CN)(OH)	2.26
CH ₃ OCH ₂ ·	3.64	CF ₃ ·	-4.17
FCH ₂ ·	-1.89	CCl ₃ ·	-13.79
(CH ₃) ₂ CH·	2.57	CH ₂ =CH-CH ₂ ·	13.28
(NC) ₂ CH·	5.17	C ₆ H ₅ -CH ₂ ·	12.08
(HO) ₂ CH·	-2.05	CH ₂ =CH·	-6.16
		HC≡C·	-15.57
		C ₆ H ₅ ·	-10.27
		C ₅ H ₅ ·	19.24
		CH ₃ C· O	7.10

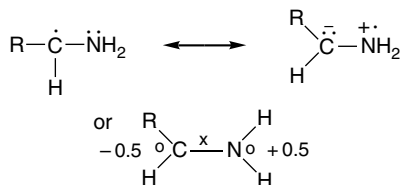
a. Stabilization energy as defined by G. Leroy, D. Peeters, and C. Wilante, *Theochem*, **5**, 217 (1982).

SECTION 3.4

Electronic Substituent
Effects on Reaction
Intermediates



illustrated by considering the effects on two types of compounds that exhibit significant radical stabilization, namely amines and compounds with captodative stabilization.

The CH bond dissociation energies of amines are particularly interesting and significant. The radical can be stabilized by interaction with the nitrogen unshared pair.

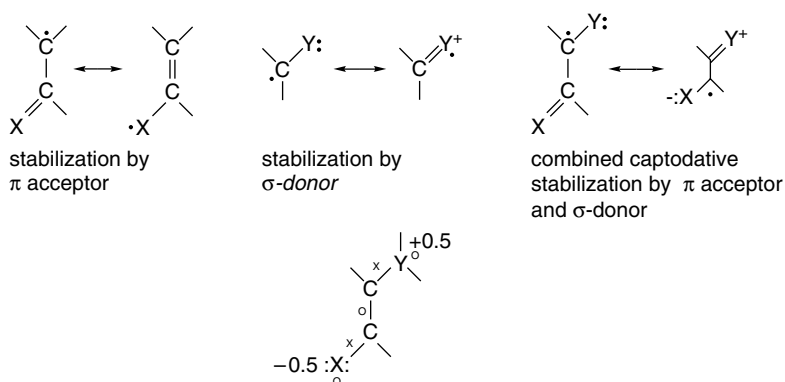


However, the same interaction—hyperconjugation—is present in the parent amine, as revealed by spectroscopic features of the C—H bond (see Section 1.1.8). Recent direct measurements have been made for (CH₃)₃N and (CH₃CH₂)₃N, as well as the pyrrolidine and piperidine, among others.¹⁰² The results obtained are shown below. The recommended value for the RSE for the aminomethyl radical is 13 ± 1 kcal/mol. Similar results were obtained using G2(MP2) calculations with isodesmic reactions. Pyrrolidine, the five-membered cyclic amine, has a slightly larger RSE because there is some relief of eclipsing interactions in the radical.

¹⁰². (a) D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu, and D. A. Armstrong, *J. Am. Chem. Soc.*, **119**, 8925 (1997); (b) J. Lalevee, X. Allonas, and J.-P. Fouassier, *J. Am. Chem. Soc.*, **124**, 9613 (2002).

<i>pri</i>	BDE	RSE	<i>sec</i>	BDE	RSE	<i>tert</i>	BDE	RSE
H ₂ NCH ₂ —H	93.9	12.2	(CH ₃) ₂ NH	87.0	12.7	(CH ₃) ₃ N	92.5	12.4
H ₂ NCH ₂ —H CH ₃	90.0	13.1		90.0	14.8	Et ₃ N	91.0	13.8
H ₂ NC(CH ₃) ₂ —H	88.9	12.2		92.0	12.9	Bu ₃ N	91.0	13.8

Captodative radicals have both electron donor and electron acceptor substituents at the radical center. The separate stabilizing effects of these substituents appear to have the ability to be synergistic. A Linnett structure gives a similar representation.



The Leroy analysis has been applied to captodative systems.¹⁰³ Table 3.18 shows the radical RSE calculated for some captodative radicals. An interesting aspect of the data is the failure of cyano groups to provide captodative stabilization. A significant consequence of the captodative effect is that the C—H bond of α -amino derivatives of acids, esters, aldehydes, and ketones are expected to be very significantly weakened,

Table 3.18. Stabilization Energy for Some Captodative Radicals (in kcal/mol)^a

HO— $\dot{\text{C}}\text{H}$ —CN	−3.40
HO— $\dot{\text{C}}\text{H}$ —CH=O	7.10
HO— $\dot{\text{C}}\text{H}$ —CO ₂ H	5.01
HO— $\dot{\text{C}}\text{H}$ —NO ₂	0.03
H ₂ N— $\dot{\text{C}}\text{H}$ —CN	0.25
H ₂ N— $\dot{\text{C}}\text{H}$ —CH=O	6.86
H ₂ N— $\dot{\text{C}}\text{H}$ —CO ₂ H	7.72
H ₂ N— $\dot{\text{C}}\text{H}$ —NO ₂	3.97

a. From G. Leroy, J. P. Dewispelaere, H. Benkadou, D. R. Temsamani, and C. Wilante, *Bull. Chim. Soc. Belg.*, **103**, 367 (1994).

¹⁰³ G. Leroy, J. P. Dewispelaere, H. Benkadou, D. R. Temsamani, and C. Wilante, *Bull. Soc. Chim. Belg.*, **103**, 367 (1994); G. Leroy, M. Sana, and C. Wilante, *Theochem*, **234**, 303 (1991).

falling in the range 75–80 kcal, which is weaker than either allylic or benzylic bonds. Because of the prevalence of such bonds in peptides and proteins, the strength of the C–H bonds of α -amido carboxamides is of substantial biological interest.¹⁰⁴

The stabilization provided by various functional groups contributes to reduced BDEs for bonds to the stabilized radical center. Computational methods can be used to assess these effects. The BDE can be calculated by comparing the total energy of the dissociated radicals with the reactant. Differences in bond dissociation energies relative to methane (Δ BDE) can be taken as a measure of the stabilizing effect of the substituent on the radical. Some computed Δ BDE values are given in Table 3.19 and compared with experimental values. As an example of the substituent effect on BDEs, it can be seen that the primary C–H bonds in acetonitrile (12 kcal/mol) and acetone (11 kcal/mol) are significantly weaker than a primary C–H bond in methane. The data show that both electron-releasing and electron-withdrawing functional groups stabilize radicals. The strong bond-weakening effect of amino substituents is noteworthy, both in its size and the apparent underestimation of this effect by the computations. A recent reevaluation of the Δ BDE for amines arrived at a value of 13 ± 1 kcal/mol, which is in better agreement with the calculations.^{102b}

Theoretical calculations on radical stability entail some issues that are not present in diamagnetic molecules. These complications originate from the need to account for the singly occupied orbital. A comparison assessed the ability of a range of computational methods to reproduce radical stabilization energies.¹⁰⁵ A variant of the CBS-Q method called CBS-RAD was found adequate for calculation of geometry and energy of the $\text{FCH}_2\cdot$, $\text{CH}_2=\text{CF}\cdot$, and $\text{NCCH}_2\cdot$ radicals. This method, along with others,

Table 3.19. Substituent Stabilization Relative to the Methyl Radical (in kcal/mol)

Substituent	Δ BDE ^a	AUMP2 ^b	B3LYP/6-31+G ^c	G3(MP2)RAD ^d	CBS-RAD ^d
H	0.0	0.0	0.0	0.0	0.0
CH ₃	7	3.2	4.8	3.4	3.8
CH ₂ =CH	19	12.6	18.8	16.9	17.6
C ₆ H ₅	17				
HC=O		9.5		8.3	9.6
CH ₃ C=O	11		9.2		
C ₆ H ₅ C=O	12				
CO ₂ C ₂ H ₅	10			5.1	6.0
CN	12	6.7	10.4	7.6	8.9
NO ₂	7			2.8	3.3
F	3	5.0		3.0	3.3
CH ₃ O	12	8.9(OH)	9.8	7.4	8.2
NH ₂	22	11.1	13.3	10.6	11.6
(CH ₃) ₂ N	21				

a. F. G. Bordwell, X. -M. Zhang, and M. S. Alnajjar, *J. Am. Chem. Soc.*, **114**, 7623 (1992); F. G. Bordwell and X. -M. Zhang, *Acc. Chem. Res.*, **26**, 570 (1993).

b. M. Lehd and F. Jensen, *J. Org. Chem.*, **56**, 884 (1991).

c. B. S. Jursic, J. W. Timberlake, and P. S. Engel, *Tetrahedron Lett.*, **37**, 6473 (1996).

d. D. J. Henry, C. J. Parkinson, P. M. Mayer, and L. Radom, *J. Phys. Chem. A*, **105**, 6750 (2001).

¹⁰⁴. P. E. M. Siegbahn, M. R. A. Blomberg, and R. H. Crabtree, *Theoretical Chem. Acc.*, **97**, 289 (1997); P. A. Frey, *Annu. Rev. Biochem.*, **70**, 121 (2001); G. Sawyers, *FEMS Microbiological Rev.*, **22**, 543 (1998).

¹⁰⁵. P. M. Mayer, C. J. Parkinson, D. M. Smith, and L. Radom, *J. Chem. Phys.*, **108**, 604 (1998).

was then applied to a wider range of radicals. G3(MP2), AUMPQ, and B3LYP/6-31+G methods are also satisfactory. Some of these data are included in Table 3.19.

Table 3.20 provides some other comparisons. The first column gives experimental BDEs derived from thermodynamic data. The other columns give ΔH calculated for the dissociative reaction, using various computational methods:



The computations that do not include electron correlation (HF) lead to large errors, but the other current methods that are applicable to molecules of this size perform satisfactorily.

Comparison of the thermochemical, kinetic, and computational evaluation of radical substituent effects provides a consistent picture. Delocalization, as in allylic and benzylic systems, provides ~ 15 kcal/mol of stabilization. Conjugated EWGs such as acyl and cyano provide significant stabilization, usually in the range of 5–10 kcal/mol. Oxygen and especially nitrogen groups provide stabilization as well. In contrast, the sp^2 and sp C–H bonds directly on vinyl, aryl, and alkynyl carbons are difficult to break, and the corresponding radicals are considered to be destabilized. An interesting contrast to these are acyl radicals, which are relatively easily formed from aldehydes by hydrogen atom abstraction (see Section 11.4.3). Stabilization results from conjugation with the oxygen electrons. These radicals are isoelectronic with NO and like NO, a Linnett-type structure can be drawn for acyl radicals. Showing a bond order of 2.5.

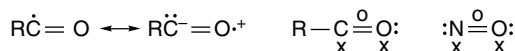


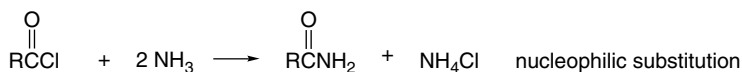
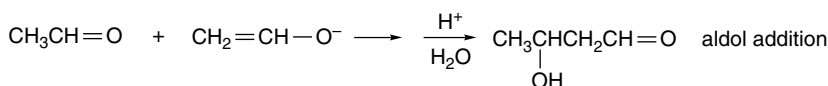
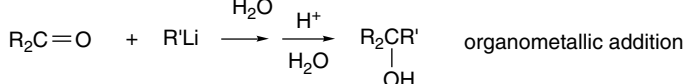
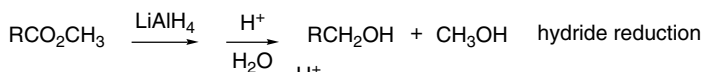
Table 3.20. Comparison of Experimental and Calculated C–H Bond Dissociation Energies for Hydrocarbons and Representative Derivatives (in kcal/mol)

Compound	Experimental	Theoretical BDE						
		BDE (av.) ^a	HF/6-31G(d,p)	MP2/6-31G(d,p)	CBS-4 ^b	CBS ^b	G2(MP2) ^b	G2 ^b B3LYP/6-31G(d,p)
H–H	104.2		79.5	95.8			104.0	106.4
CH ₃ –H	104.8		79.4	100.3	103.6	103.3	104.0	105.8
CH ₃ CH ₂ –H	101.1		76.8	98.9	99.9	100.0	100.0	101.1
(CH ₃) ₂ CH–H	97.6		74.5	95.3	97.0	97.4	98.4	97.1
CH ₃) ₃ C–H	96.5		72.7	93.7				94.0
CH ₂ =CHCH ₂ –H	84.9		85.0	87.5		87.3		
FCH ₂ –H	101.7		77.8	96.0			99.1	
ClCH ₂ –H	101.5		76.6	95.0			99.7	
HOCH ₂ –H	96.2		74.1	92.3	95.6	95.3	96.2	95.2
H ₂ NCH ₂ –H	92.2		67.5	85.0	91.8	91.9	93.1	87.7
HSCH ₂ –H	94.1		74.9	93.1			96.3	
NCCH ₂ –H	93.4		69.8	96.2			93.8	
O=CHCH ₂ –H	94.2		67.3	93.5			93.4	
CH ₃ COCH ₂ –H	95.1		69.4	94.4			94.0	
HO ₂ CCH ₂ –H	96.0		73.7	95.2			97.2	
CH ₃ SO ₂ CH ₂ –H	99.0		80.8	101.2			103.4	
Cl ₃ C–H	95.6		71.8	89.4			92.0	

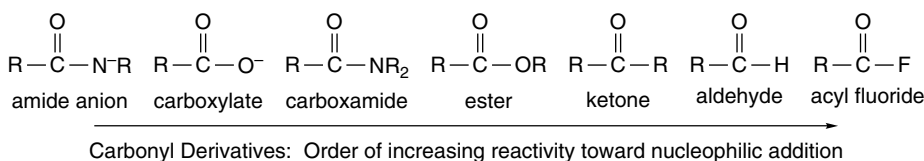
a. H.-G. Korth and W. Sicking, *J. Chem. Soc., Perkin Trans.*, **2**, 715 (1997).

b. J. W. Ochterski, G.A. Petersson, and K. B. Wiberg, *J. Am. Chem. Soc.*, **117**, 11299 (1995).

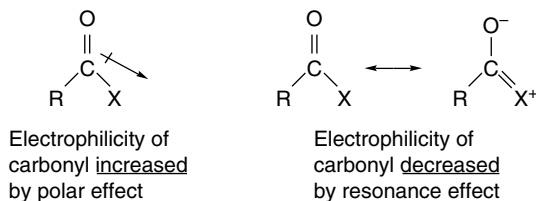
Addition of nucleophiles to carbonyl groups constitutes a very important class of reactions. A wide variety of reactions fall into this category, including hydride reductions, organometallic additions, aldol additions, and the nucleophilic substitution (including, e.g., hydrolysis, esterification, and aminolysis) reactions of carboxylic acid derivatives. We focus attention on the latter group of reactions at this point, because they are familiar from introductory organic chemistry and illustrate important substituent effects on carbonyl group reactivity. Nucleophilic substitution reactions of carboxylic acid derivatives also serve to emphasize the point that substituents can influence reaction rates through effects on reactants as well as on transition states and intermediates.



The major classes of carbonyl compounds include aldehydes, ketones, carboxamides, esters, carboxylic acids and anhydrides, and carbonyl halides (acyl halides). These groups differ in the identity of the substituent X on the carbonyl group. At this point we concentrate on these examples, but a number of other carbonyl derivatives have important roles in synthetic and/or biological reactions. These other compounds include acyl cyanides, acyl azides, *N*-acylimidazoles, *O*-aryl esters, and thioesters. The carbonyl compounds are arranged below in the order of the increasing reactivity toward nucleophilic addition.



At this point we want to consider the relative reactivity of carboxylic acid derivatives and other carbonyl compounds in general terms. We return to the subject in more detail in Chapter 7. Let us first examine some of the salient structural features of the carbonyl compounds. The strong polarity of the C=O bond is the origin of its reactivity toward nucleophiles. The bond dipole of the C–X bond would be expected increase carbonyl reactivity as the group X becomes more electronegative. There is another powerful effect exerted by the group X, which is resonance electron donation.



Substituents with unshared electrons allow electron delocalization, which stabilizes the compound and increases the negative charge on oxygen. This resonance effect stabilizes the carbonyl compound and decreases the reactivity of the carbonyl group toward nucleophiles. The order of electron donation by resonance is $\text{RN}^- > \text{O}^- > \text{NR}_2 > \text{OR} \sim \text{OH} > \text{F}$. The trends in the resonance and polar effects of these substituents are *reinforcing* and lead to the overall reactivity trends shown above. The amido group is the strongest resonance donor and weakest polar acceptor, whereas the fluorine is the weakest π donor and strongest σ acceptor.

There have been several attempts to analyze these substituent effects using computational approaches. For example, the isodesmic reaction



yields the results shown in Table 3.21.¹⁰⁶ In this formulation, the total stabilization includes both the differences between the C–X and the C–C bond strength and the resonance stabilization of the substituent. Remember (Section 3.1.2.2) that the C–X bond strength increases because of electronegativity differences. An indication of the extent of the π conjugation can be obtained from the C–X π bond orders shown in Figure 3.20. The $\text{C}=\text{X}^+$ bond order decreases in the series $\text{NH}_2(0.28) > \text{OCH}_3(0.22) > \text{F}(0.13)$. These values can be contrasted to those for $\text{C}\equiv\text{N}$ and CH_3 , where there is minimal π delocalization and the π bond orders are around 0.04. Figure 3.20 also shows the atomic charges, as determined by the AIM method.

It is also desirable to separate the resonance component of the total stabilization energy. Wiberg addressed the issue by comparing total stabilization with the rotational barrier, which should be a measure of the resonance contribution.¹⁰⁷ The resonance component for F was assumed to be zero. This analysis provides the order $\text{NH}_2 > \text{OH}$ for the π stabilization but $\text{OH} > \text{NH}_2$ for the σ component, as shown in Table 3.22.

Table 3.21. Carbonyl Substituent Stabilization as Estimated by Isodesmic Replacement by Methyl (in kcal/mol)^a

Substituent	ΔH_{exp}	HF/6-31G*	MP2/6-31G*	MP3/6-311 + +G**
NH ₂	19.6	20.6	21.2	18.3
OH	23.4	25.5	26.8	22.3
F	17.9	19.0	21.1	16.4
SiH ₃		−13.0	−12.0	−12.6
PH ₂		−6.2	−3.5	−3.9
SH	4.5	4.3	7.3	5.5
Cl	6.6	2.9	7.9	6.7
CN		−11.8	−9.3	−11.0
CF ₃		−11.9	−11.0	−12.4

a. Data from K. B. Wiberg, C. M. Hadad, P. R. Rablen, and J. Cioslowski, *J. Am. Chem. Soc.*, **114**, 8644 (1992).

¹⁰⁶ K. B. Wiberg, C. M. Hadad, P. R. Rablen, and J. Cioslowski, *J. Am. Chem. Soc.*, **114**, 8644 (1992).

¹⁰⁷ K. B. Wiberg, *Acc. Chem. Res.*, **32**, 922 (1999); K. B. Wiberg, *J. Chem. Educ.*, **73**, 1089 (1996).

(a) Charge density

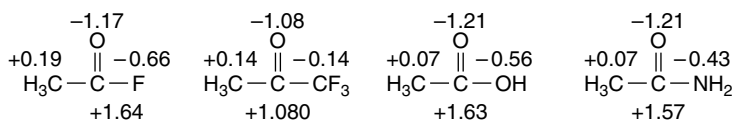
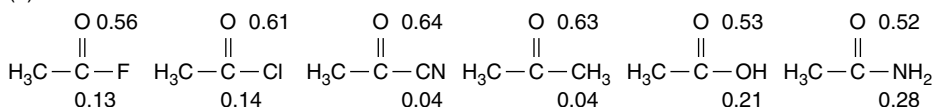
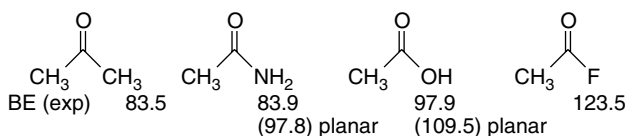
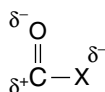
(b) π -Bond order

Fig. 3.20. Charge density (a) and bond orders (b) for carbonyl derivatives.

The bond energies of the $\text{O}=\text{C}-\text{X}$ bonds increase sharply with electronegativity. For NH_2 and OH there are different values for perpendicular and planar structures, reflecting the resonance contribution to the planar form.



The increasing $\text{C}-\text{X}$ bond strength (apart from resonance) is attributed to the electrostatic attraction associated with the difference in electronegativity. This is accentuated by the already existing $\text{C}=\text{O}$ charge separation and leads to a favorable juxtaposition of positive and negative charge.¹⁰⁸



There have been several attempts¹⁰⁹ to assign relative importance to the polar (including electrostatic) and resonance components of the stabilization carboxylate

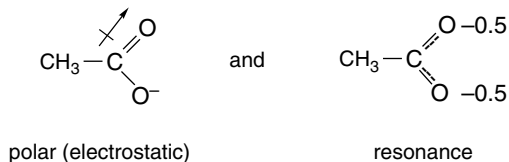
Table 3.22. Separation of the Resonance Component of the Stabilization Energy

	Total SE	ΔH_{rot}	ΔH_{σ}
F	16.7	—	16.7
OH	27.7	11.5	16.2
NH_2	19.3	13.9	5.4
Cl	6.8	—	6.8
SH	6.1	8.1	-2.0
PH_2	-3.9	0	-3.9
SiH_3	-12.7	0	-12.7

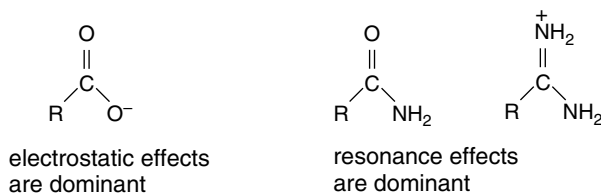
¹⁰⁸. J. B. Levy, *Struct. Chem.*, **10**, 121 (1999).

¹⁰⁹. P. C. Hiberty and C. P. Byrman, *J. Am. Chem. Soc.*, **117**, 9875 (1995); R. W. Taft, I. A. Koppel, R. D. Topsom, and F. Anvia, *J. Am. Chem. Soc.*, **112**, 2047 (1990); M. R. F. Siggel, A. Streitwieser, Jr., and T. D. Thomas, *J. Am. Chem. Soc.*, **110**, 8022 (1988).

anions. In a comparison of the acidity of acetic acid (p*K* 4.7) with that of alcohols (p*K* 16–18), the issue is the relative importance of the C=O bond dipole and resonance in stabilizing the carboxylate anion. These approaches have led to estimates ranging from 50 to 80% of the stabilization being polar in origin.



Rablen¹¹⁰ investigated carbonyl substituent effects by using a series of isodesmic reactions designed to separate resonance and polar effects. He found the oxygen π contributions to be about 6 kcal/mol, as opposed to about 14 kcal/mol for nitrogen. The order of the polar effect is $F > O > N > C$, whereas that for the resonance effect is $N > O > F$. His analysis suggests that the stabilization in acetate (O^- donor) is about one-third resonance and two-thirds electrostatic. On the other hand, in amides and amidines, the order is reversed, roughly two-thirds resonance and one-third electrostatic.



A physical property that reflects the electronic character of the carbonyl substituent is the ^{17}O NMR chemical shift. Although the relation of the chemical shift to electronic properties is complex, there is a correlation with the resonance electron-donating ability of the substituent. The π -donor substituents cause large downfield shifts in the order $Cl \ll F < OCH_3 < NH_2$. Nonconjugating substituents, such as cyano, trifluoromethyl, and methyl, have much smaller effects (Table 3.23).

Table 3.23. ^{17}O Chemical Shifts for CH_3COX^a

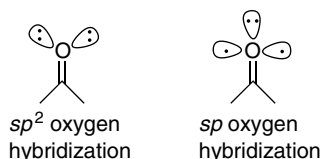
X	^{17}O
CN	603 ^b
CF ₃	592
H	592
CH ₃	571
Cl	502
F	374
CH ₃ O	361
NH ₂	313

a. H. Dahm and P. A. Carrupt, *Magn. Reson. Chem.*, **35**, 577 (1997).

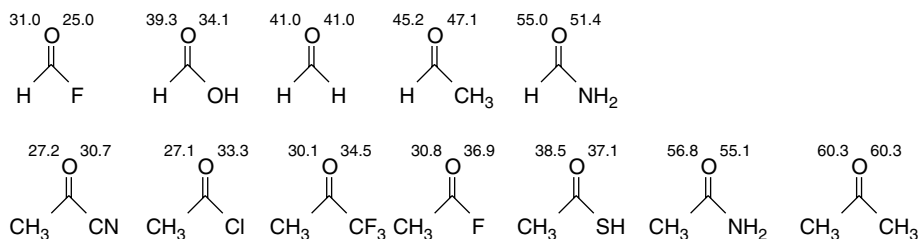
b. J.-C. Zhuo, *Molecules*, **4**, 320 (1999).

¹¹⁰ P. R. Rablen, *J. Am. Chem. Soc.*, **122**, 357 (2000).

Another important aspect of carbonyl group structure and reactivity is associated with the two pairs of unshared electrons at the oxygen. These are usually formulated as occupying two sp^2 , rather than one p and one sp orbital.

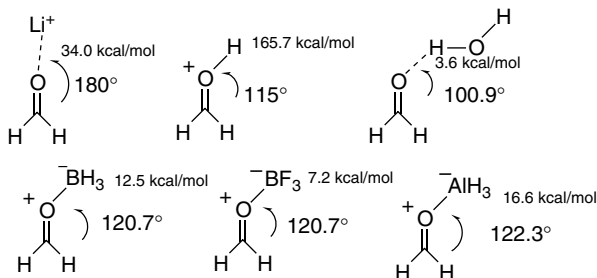


Wiberg and co-workers calculated the electrostatic potential at the carbonyl oxygen for several derivatives at the MP2/6-31 + G* level.¹¹¹ The most negative electrostatic potential is found at angles somewhat greater than 120° , but generally corresponding with the trigonal sp^2 hybridization model.



Note that the unsymmetrical compounds have somewhat different potentials *syn* and *anti* to the substituent. The qualitative order found for the formyl series $F < OH < H < CH_3 < NH_2$ suggests a mixture of σ polar effects and π -electron donation. The acetyl series also included CN, Cl, and SH. It is interesting that the fluoride is calculated to have a more negative potential at oxygen than the chloride. This indicates a resonance contribution that attenuates the σ polar effect.

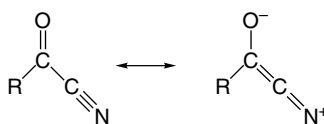
The reactivity of carbonyl groups is strongly influenced by interactions between protons or Lewis acids and the carbonyl oxygen unshared electrons. Wiberg and co-workers computationally probed the interaction of the carbonyl oxygen with Li^+ , H^+ , and water (hydrogen bonding). Whereas Li^+ prefers a linear structure, indicating that the attraction is primarily electrostatic rather than directional bonding, both protonation and hydrogen bonding favored the trigonal geometry. The same was true for the Lewis acids, BH_3 , BF_3 , and AlH_3 . The bonding energy was also calculated. Note the wide range of bond strengths from hydrogen bonding (3.6 kcal/mol) to formation of a very strong bond by protonation (165.7 kcal/mol). The calculated bond strengths for the Lewis acids is much smaller.



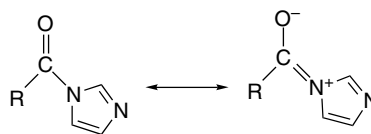
¹¹¹ K. B. Wiberg, M. Marquez, and H. Castejon, *J. Org. Chem.*, **59**, 6817 (1994).

Other workers examined hydrogen bonding of HF with carbonyl compounds. There is good correlation between the strength of the hydrogen bond (1–8 kcal/mol) and the electrostatic potential at the carbonyl oxygen.¹¹² Thus one important factor in carbonyl group reactivity is the potential for interaction with protons and Lewis acids, including metal ions.

We can summarize the structural effects of the substituents at the carbonyl group in terms of the resonance and polar contributions. While there may be variation in the relative weighting assigned to the polar and resonance components, the general trends are clear. Electron pair donors interact with the carbonyl group by resonance and the order of electron donation is $C:^- > HN^- > O^- > H_2N > RO > F$. The polar effect owing to substituent electronegativity is in the opposite direction, with $F > RO > H_2N$. These effects are *reinforcing* and increase carbonyl reactivity in the order $C:^- < HN^- < O^- < H_2N < RO < F$. The consequences of these resonance and polar effects on the carbonyl group can be observed in various ground state, i.e., reactant, properties. Groups such as cyano and imidazolidine that have very weak resonance stabilization are dominated by the polar effect of the substituent and are quite reactive toward nucleophiles.



Cyano is very poor
resonance donor

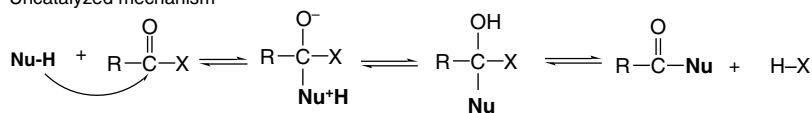


Imidazole aromaticity minimizes
resonance donation by nitrogen

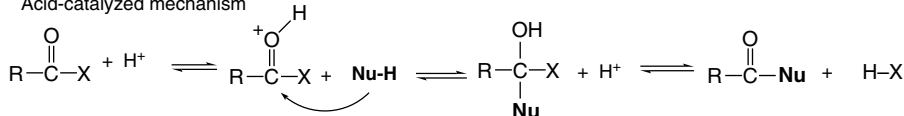
Let us now examine how substituent effects in *reactants* influence the rates of nucleophilic additions to carbonyl groups. The most common mechanism for substitution reactions at carbon centers is by an *addition-elimination mechanism*. The adduct formed by the nucleophilic addition step is tetrahedral and has sp^3 hybridization. This adduct may be the product (as in hydride reduction) or an intermediate (as in nucleophilic substitution). For carboxylic acid derivatives, all of the steps can be reversible, but often one direction will be strongly favored by product stability. The addition step can be acid-catalyzed or base-catalyzed or can occur without specific catalysis. In protic solvents, proton transfer reactions can be an integral part of the mechanism. Solvent molecules, the nucleophile, and the carbonyl compound can interact in a concerted addition reaction that includes proton transfer. The overall rate of reaction depends on the reactivity of the nucleophile and the position of the equilibria involving intermediates. We therefore have to consider how the substituent might affect the energy of the tetrahedral intermediate.

¹¹² P. Bobadova-Parvanova and B. Galabov, *J. Phys. Chem. A.*, **102**, 1815 (1998); J. A. Platts, *Phys. Chem. Phys.*, **2**, 3115 (2000).

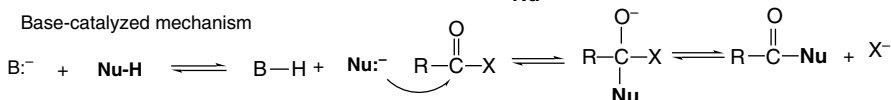
Uncatalyzed mechanism



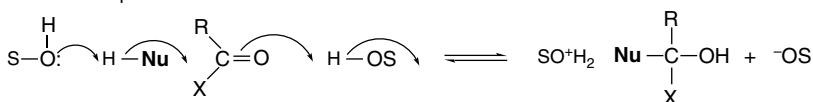
Acid-catalyzed mechanism



Base-catalyzed mechanism



Concerted proton transfer



Some time ago, J. P. Guthrie derived an energy profile pertaining to the hydrolysis of methyl acetate under acidic, neutral, and basic conditions from kinetic data.¹¹³ These reaction profiles are shown in Figure 3.21. This reaction can serve to introduce the issues of relative reactivity in carbonyl addition reactions. The diagram shows that the reaction is nearly energetically neutral in acidic solution, but becomes exothermic in neutral and basic solutions because of the additional stabilization associated with the carboxylate group. The activation barrier is highest for the neutral reaction. The activation barrier is lowered in acidic solution as a result of the enhanced reactivity of the protonated carbonyl (acid-catalyzed mechanism). The activation barrier for the basic hydrolysis is reduced because hydroxide ion is a more powerful nucleophile than water (base-catalyzed mechanism).

The energy relationships among reactants, transition states, intermediates, and products have been further explored for the base-catalyzed hydrolysis of methyl acetate.¹¹⁴ The relative energies of the species shown in Figure 3.22 were calculated using

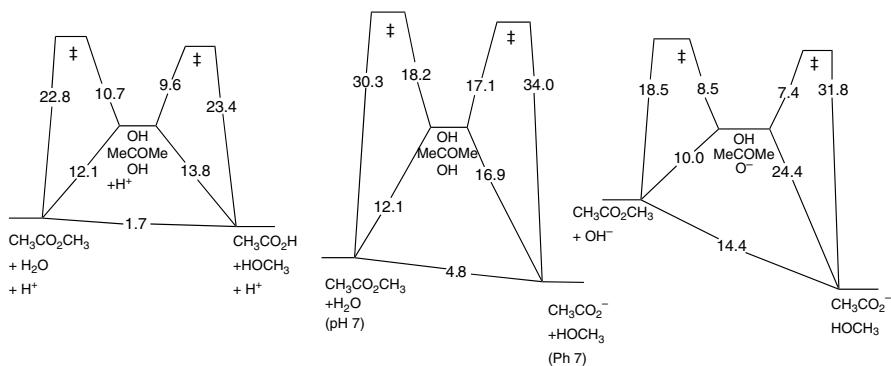


Fig. 3.21. Comparative reaction energy profiles for acidic, neutral, and basic hydrolysis of methyl acetate in water. Adapted from *J. Am. Chem. Soc.*, **95**, 6999 (1973), by permission of the American Chemical Society.

¹¹³. J. P. Guthrie, *J. Am. Chem. Soc.*, **95**, 6999 (1973).

¹¹⁴. C.-G. Zhan, D. W. Landry, and R. L. Ornstein, *J. Am. Chem. Soc.*, **122**, 1522 (2000).

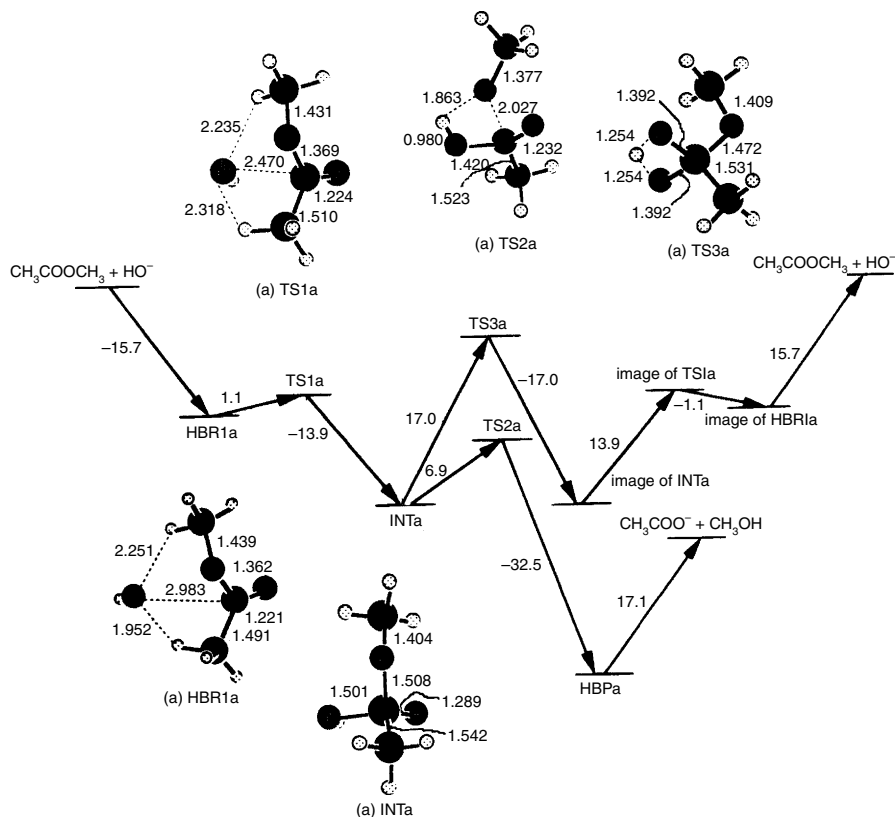
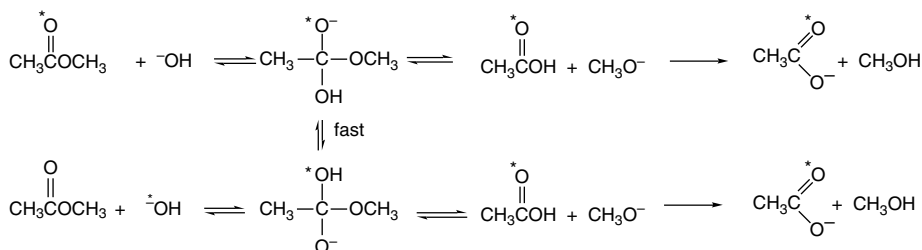


Fig. 3.22. Energy profiles (in kcal/mol) and structures of intermediates and transition states for competing hydrolysis and carbonyl oxygen exchange for methyl acetate and hydroxide ion in the gas phase. Adapted from *J. Am. Chem. Soc.*, **122**, 1522 (2000), by permission of the American Chemical Society.

several MO and DFT computations. The values quoted are for BLYP/6-31++G(*d,p*) level calculations and refer to the gas phase. These energy values describe both the hydrolysis reaction and the carbonyl oxygen exchange reaction, both of which occur through the same tetrahedral addition intermediate. **HBR1a** is a complex between OH^- and the reactant. **TS1a** and **INTa** are the TS and tetrahedral intermediate, respectively, resulting from hydroxide addition. **TS2a** is the TS leading to methoxide elimination, which results in the stable complex of methanol and acetate ion. **TS3a** is the TS for proton transfer between the two oxygens, which leads to oxygen exchange via an intermediate that is structurally identical to **TS1a**.



This theoretical examination of carbonyl addition reactions serves to emphasize the enormous role that solvation effects play. As indicated in Figure 3.22 and other studies, gas phase addition of hydroxide ion to esters is calculated to be *exothermic* and to encounter only a very small barrier at **TS1a** and **TS2a**.¹¹⁵ The major contribution to the activation barrier (18.5 kcal/mol) that is observed in solution is the energy of desolvation of the hydroxide ion.¹¹⁶ We return to a discussion of solvation effects on carbonyl additions in Section 3.8.

A similar comparison of the gas phase and solution phase reaction of *N,N*-dimethylacetamide was conducted.¹¹⁷ Energies were calculated at the MP2/6-31 + G** level. Solution phase calculations were done using a continuum solvent model. The results are summarized in Figure 3.23 and, as with the ester reaction, the addition is calculated to be exothermic in the gas phase, but to have a barrier in solution. Interestingly, the HF/6-31 + G** energy values are somewhat closer to the experimental values than the MP2/6-31 + G** results. The solution value is 24.6 kcal/mol.¹¹⁸

Similar energy profiles for the other classes of carbonyl compounds would allow us to make broad comparisons in reactivity. Unfortunately, the reactivity covers a very

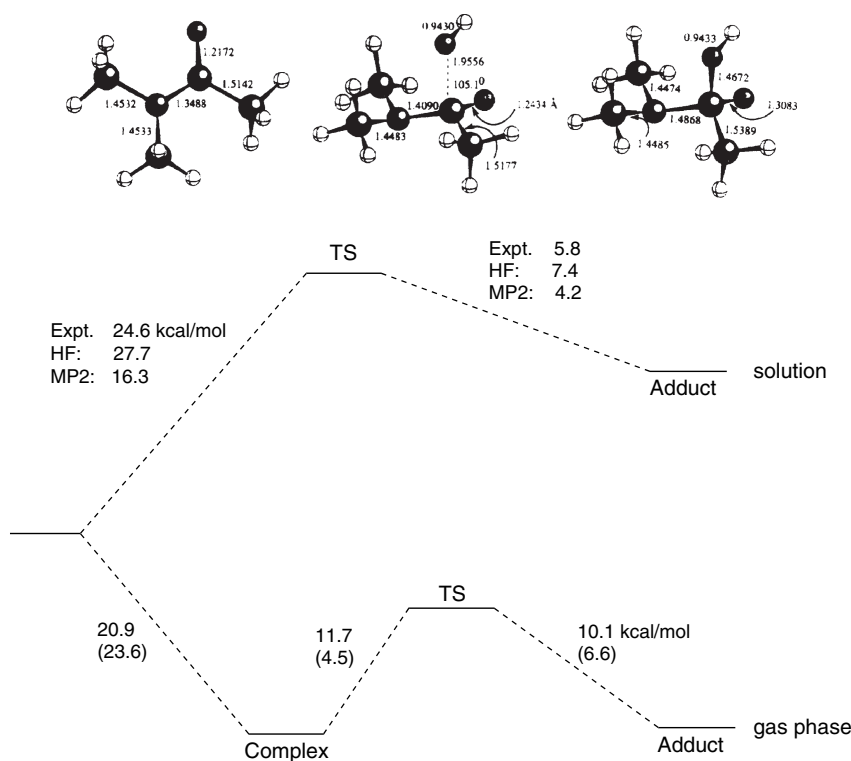


Fig. 3.23. Gas phase and solution reaction energy profiles for addition of hydroxide ion to *N,N*-dimethylacetamide. MP2 values are in paranthese Adapted from *Theochem*, **429**, 41 (1998), by permission of Elsevier.

¹¹⁵. K. Hori, *J. Chem. Soc., Perkin Trans.*, **2**, 1629 (1992); I. Lee, D. Lee, and C. K. Kim, *J. Phys. Chem. A*, **101**, 879 (1997); F. Hæfner, C.-H. Hu, T. Brink, and T. Norin, *Theochem*, **459**, 85 (1999).

¹¹⁶. M. J. S. Dewar and D. M. Storch, *J. Chem. Soc., Chem. Commun.*, 94 (1985); J. P. Guthrie, *Can. J. Chem.*, **68**, 1643 (1990).

¹¹⁷. Y.-J. Zheng and R. L. Ornstein, *Theochem*, **429**, 41 (1998).

¹¹⁸. J. P. Guthrie, *J. Am. Chem. Soc.*, **96**, 3608 (1974).

wide range and it is not easy to make direct experimental comparisons. In Scheme 3.2 some available kinetic data are provided that allow at least a qualitative comparison of the reactivity of the most common derivatives. The ratio of reaction toward hydroxide is anhydride > ester > amide, reflecting the expected trend and is dominated by the resonance effect. Acyl chlorides are even more reactive, judging by a comparison of methanolysis and hydrolysis. The data for esters give the nucleophilicity order as $^-\text{OH} > \text{NH}_3 > \text{H}_2\text{O}$, as expected.

A more extensive and precise set of data has been developed that includes aldehydes and ketones (but not acyl halides), which pertains to the equilibrium constant for hydration.¹¹⁹

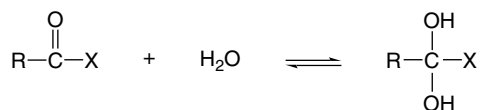


Table 3.24 shows the values for equilibrium constants for nucleophilic addition of both water and hydroxide ion. We can see the following trends in these data: For aldehydes and ketones, the addition is disfavored in the order $\text{Ph} > \text{alkyl} > \text{H}$. The order $\text{NH}_2 < \text{OR} < \text{CH}_3 < \text{H}$ is indicated by the K_{hydr} values of $10^{-13.8}$, $10^{-6.6}$, $10^{0.03}$, and $10^{3.36}$ for *N,N*-dimethylformamide, methyl formate, acetaldehyde, and formaldehyde,

Scheme 3.2. Relative Reactivity Data for Some Carboxylic Acid Derivatives

	$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\text{Cl}$	$(\text{CH}_3\overset{\text{O}}{\parallel}{\text{C}})_2\text{O}$	$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}'$	$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2$
Hydrolysis (^-OH)		$8.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ at 25° C (a)	$2.2 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ at 0° C $E_a = 18.5$ (b)	$1.8 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ $E_a = 24.1$ (c)
Hydrolysis (H_2O)		$2.4 \times 10^{-3} \text{ s}^{-1}$ at 25° C (a)	$3 \times 10^{-10} \text{ s}^{-1}$ at 0° C $E_a = 30.2 \text{ kcal(b)}$	
Methanolysis (CH_3OH)	$1 \times 10^{-1} \text{ s}^{-1}$ at 0° C (d)			
Aminolysis (NH_3)			$2.8 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$ in 10 M H_2O in dioxane (e) $3.7 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$ in 5 M $\text{HOCH}_2\text{CH}_2\text{OH}$ in dioxane (f)	

a. C. Castro and E. A. Castro, *J. Org. Chem.*, **46**, 2939 (1981); J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 837 (1964).

b. J. P. Guthrie, *J. Am. Chem. Soc.*, **95**, 6999 (1973).

c. J. P. Guthrie, *J. Am. Chem. Soc.*, **96**, 3608 (1974).

d. T. W. Bentley, G. Llewellyn, and J. A. McAlister, *J. Org. Chem.*, **61**, 7927 (1996).

e. F. H. Wetzel, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **75**, 1150 (1953).

f. E. M. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950).

¹¹⁹. J. P. Guthrie, *J. Am. Chem. Soc.*, **122**, 5529 (2000).

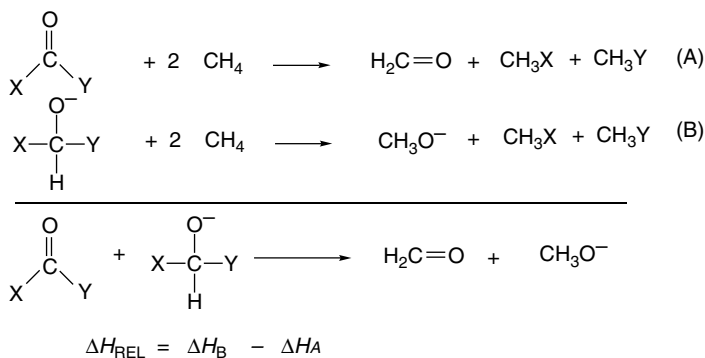
Table 3.24. Equilibrium Constants for Hydration and Hydroxide Addition for Selected Carbonyl Compounds

Compounds ^a	log $K_{\text{H}_2\text{O}}$	log $K_{-\text{OH}}$
$\text{CH}_2=\text{O}$	3.36	6.51
$\text{CH}_3\text{CH}=\text{O}$	0.03	4.68
$(\text{CH}_3)_2\text{CHCH}=\text{O}$	-0.21	2.99
$\text{PhCH}=\text{O}$	-2.10	2.5
$(\text{CH}_3)_2\text{C}=\text{O}$	-2.85	2.04
HCO_2CH_3	-6.6	1.58
$\text{CH}_3\text{CO}_2\text{CH}_3$	-8.2	-0.82
$(\text{CH}_3)_2\text{CHCO}_2\text{CH}_3$	-10.42	-1.05
$\text{CF}_3\text{CO}_2\text{CH}_3$	-0.9	5.53
HCOSC_2H_5	-3.5	2.1
$\text{CH}_3\text{COSC}_2\text{H}_5$	-8.2	-0.92
$\text{CF}_3\text{COSC}_2\text{H}_5$	-2.8	3.77
$\text{HCON}(\text{CH}_3)_2$	-13.8	-3.75
$\text{CH}_3\text{CON}(\text{CH}_3)_2$	-14.2	-4.75
$\text{CF}_3\text{CON}(\text{CH}_3)_2$	-9.2	-0.13

a. Data from J. P. Guthrie, *J. Am. Chem. Soc.*, **122**, 5529 (2000).

respectively. The hydroxide addition is in the same order but lies much further toward the adduct: $10^{-3.75}$, $10^{-0.82}$, $10^{4.68}$, and $10^{6.5}$, respectively, as expected for the stronger nucleophile. These data give a good indication of the overall reactivity of carbonyl compounds toward a prototypical nucleophilic addition, but incorporate structural effects pertaining to both the reactant and tetrahedral adduct. For example, the 100-fold difference between benzaldehyde and 2-methylpropanal presumably reflects the extra conjugative stabilization of the aromatic aldehyde. Similarly, the 10^7 and 10^5 difference between the ethyl esters and *N,N*-dimethylamides of acetic acid and trifluoroacetic acid, respectively, are due to the polar effect of the trifluoromethyl group. Note, however, that the differences are only slightly smaller ($10^{6.5}$ and $10^{4.5}$) in the anionic hydroxide adducts.

What can we say about substituent effects on the tetrahedral adducts? These have been assessed by comparing hydride affinity of the various derivatives, relative to formaldehyde,¹²⁰ using the isodesmic reaction sequence shown below.



¹²⁰ R. E. Rosenberg, *J. Am. Chem. Soc.*, **117**, 10358 (1995).

The effect of the same substituents on the adduct was evaluated by another isodesmic reaction:



This analysis permits assignment of hydride affinity to the carbonyl compounds relative to formaldehyde. The stabilization of the carbonyl compound by X relative to H is shown in Table 3.25 as $\Delta\text{C=O}$. The stabilization of the hydride adduct is shown as ΔCHO^- . The difference, the hydride affinity relative to $\text{CH}_2=\text{O}$, is listed as ΔHA . The resonance donors NH_2 and CH_3O have the largest stabilizing effect on the carbonyl starting material, but F also has a very significant stabilizing effect. The stabilization of the tetrahedral adduct is in the order of bond strength $\text{F} > \text{CH}_3\text{O} > \text{NH}_2 > \text{CH}_3$. The difference between the two values places the overall substituent effect for reactivity toward hydride in the order $\text{F} > \text{H} > \text{CH}_3 > \text{OCH}_3 > \text{NH}_2$, in excellent agreement with experimental data. The polar EWGs CN and CF_3 strongly favor hydride addition by strong stabilization of the anionic tetrahedral adduct. As a result, they have the largest overall effect on the stability of the hydride adduct, followed by fluoro and formyl.

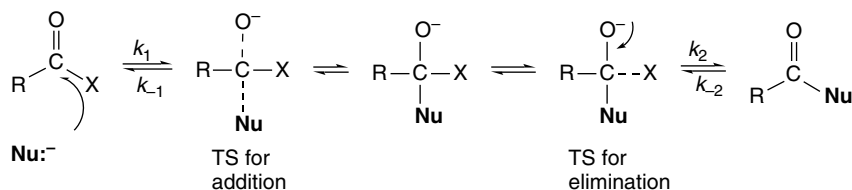
The stability relationships for carbonyl substitution reactions by an anionic nucleophile are summarized in Scheme 3.3. The simplest substitution reactions consist of two reversible steps, the formation of the tetrahedral intermediate and the subsequent elimination of the original substituent. As we discuss in Chapter 7, the mechanism is frequently more complex, often involving proton transfers. However, the stability effects of the carbonyl groups can be illustrated in terms of the simple two-step mechanisms. The stability order of reactants and products is $\text{F}, \text{Cl} < \text{OR} < \text{NR}_2 < \text{O}^-$. The order of stability of the *anionic* tetrahedral intermediates is $\text{F} > \text{RO} > \text{RN}_2 > \text{O}^-$. The diagram clearly indicates that the reactivity order will be $\text{F} > \text{RO} > \text{R}_2\text{N} > \text{O}^-$. Note also that the relative rates for the two possible fates of the tetrahedral intermediate (forward or reverse) are determined by the ease with which either X^- or Nu^- departs from the tetrahedral intermediate. This order will be $\text{F}^- > \text{RO}^- > \text{NH}_2^- > \text{O}^{2-}$, so we expect substitution on acyl fluorides (and other acyl halides) to be fast and irreversible. On the other hand, nucleophilic substitution on carboxylate anions, which is at the other end of the reactivity range, is nearly impossible. (We will see in Section 7.2.2.2 in Part B that organolithium compounds are strong enough nucleophiles to achieve addition with carboxylate groups, at least in the presence of Li^+ .) The relative stability

Table 3.25. Substituent Effects on Hydride Affinity of XYC=O by an Isodesmic Reaction Sequence (in kcal/mol by G2(MP2) Calculations)^a

X	Y	$\Delta\text{C=O}$	ΔHCO^-	ΔHA
H	H	0	0	0
H	CH_3	11.1	9.6	1.5
H	NH_2	31.5	21.8	9.7
H	CH_3O	32.8	29.0	3.8
H	F	26.1	38.2	−12.1
H	CH=O	3.1	19.0	−15.9
H	CF_3	−3.0	23.3	−26.3
H	CN	−2.4	25.9	−28.3

a. R. E. Rosenberg, *J. Am. Chem. Soc.*, **117**, 10358 (1993).

Scheme 3.3. Summary of Substituent Effects on Carbonyl Substitution Reactions

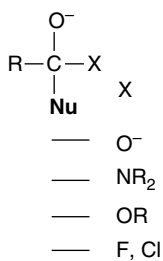


TS for addition
Based on effect of
-X on C=O reactivity

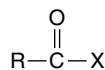
— O^- —
— R_2N —
— RO —
— F, Cl —

TS for elimination
Based on leaving group ability
of X

— O^- —
— NR_2 —
— OR —
— F, Cl —



X
— F, Cl —
— OR —
— NR_2 —
— O^- —



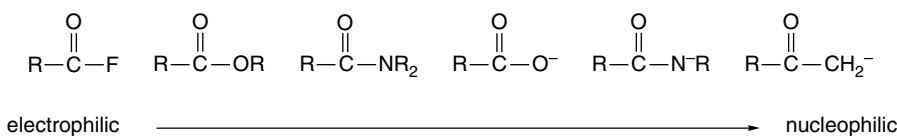
X
— F, Cl —
— OR —
— NR_2 —
— O^- —

SECTION 3.4

*Electronic Substituent
Effects on Reaction
Intermediates*

of the carboxylate starting material and the double negative charge on the tetrahedral intermediate make the activation energy for the first step very high. Even if the intermediate is formed, the prospective leaving group O^{2-} is very difficult to eliminate, so $k_{-1} > k_2$ and no substitution is observed.

Perhaps it is worth noting in summary that the series can be extended to include $\text{X}=\text{NH}^-$ and $\text{X}=\text{CH}_2^-$. These analogs would be expected to be even less reactive than carboxylate toward nucleophilic addition. The latter species is an *enolate*. We will learn in Section 7.7 that enolates are reactive nucleophiles. Carboxylate and amide anions also are nucleophilic. Even amides are somewhat nucleophilic. Going across the periodic table from F to CH_2^- , the carbonyl substituent **X** transforms the carbonyl group from an electrophile to part of a nucleophilic structure in the anionic structures by increasing electron donation.



3.5. Kinetic Isotope Effects

A special type of substituent effect that has proved very valuable in the study of reaction mechanisms is the replacement of an atom by one of its isotopes. Isotopic substitution most often involves replacing protium by deuterium (or tritium), but is applicable to nuclei other than hydrogen. The quantitative differences are largest, however, for hydrogen because its isotopes have the largest relative mass differences. Isotopic substitution usually has no effect on the qualitative chemical reactivity of the substrate, but it often has an easily measured effect on the rate, which is called a *kinetic isotope effect (KIE)*. Let us consider how this modification of the rate arises. Initially, the discussion concerns *primary kinetic isotope effects*, those in which a bond to the isotopically substituted atom is broken in the rate-determining step. We use C–H bonds as the specific case for discussion but the same concepts apply for other elements.

Any C–H bond has characteristic vibrations that impart some energy, called the *zero-point energy*, to the molecule. The energy associated with these vibrations is related to the mass of the vibrating atoms. Owing to the greater mass of deuterium, the vibrations associated with a C–D bond contribute less to the zero-point energy than the corresponding C–H bond. For this reason, substitution of protium by deuterium lowers the zero-point energy of a molecule. For a reaction involving cleavage of a bond to hydrogen (or deuterium), a vibrational degree of freedom in the normal molecule is converted to a translational degree of freedom as the bond is broken. The energy difference that is due to this vibration disappears at the transition state. The transition state has the same energy for the protonated and deuterated species. Because the deuterated molecule has the lower zero-point energy, it has a higher activation energy to reach the transition state, as illustrated in Figure 3.24.

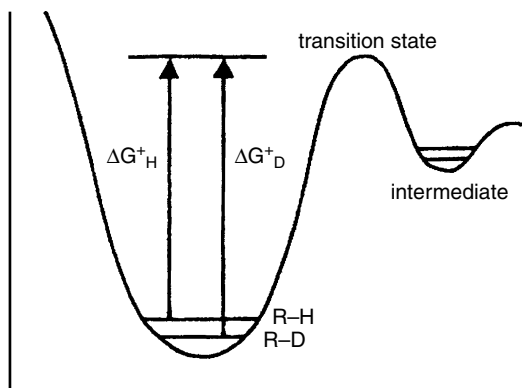
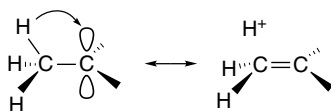


Fig. 3.24. Differing zero-point energies of protium- and deuterium-substituted molecules as the cause of primary kinetic isotope effects.

Just how large the rate difference is depends on the nature of the TSs. The maximum effect occurs when the hydrogen being transferred is bound about equally to two other atoms at the TS. The calculated maximum for the isotope effect $k_{\text{H}}/k_{\text{D}}$ involving C–H bonds is about 7 at room temperature.¹²¹ When bond breaking is more or less than half complete at the TS, the isotope effect is smaller and can be close to 1 if the TS is very reactant-like or very product-like. Primary isotope effects can provide two very useful pieces of information about a reaction mechanism. First, the existence of a substantial isotope effect, i.e., $k_{\text{H}}/k_{\text{D}} > 2$, is strong evidence that the bond to that particular hydrogen is being broken in the rate-determining step. Second, the magnitude of the isotope effect provides a qualitative indication of where the TS lies with regard to product and reactant. A relatively low primary isotope effect implies that the bond to hydrogen is either only slightly or nearly completely broken at the TS. That is, the TS must occur quite close to reactant or to product. An isotope effect near the theoretical maximum is good evidence that the TS involves strong bonding of the hydrogen to both its new and old bonding partner.

Isotope effects may also be observed when the substituted hydrogen atom is not directly involved in the reaction. Such effects, known as *secondary kinetic isotope effects*, are smaller than primary effects and are usually in the range of $k_{\text{H}}/k_{\text{D}} = 0.7 - 1.5$. They may be normal ($k_{\text{H}}/k_{\text{D}} > 1$) or inverse ($k_{\text{H}}/k_{\text{D}} < 1$), and are also classified as α or β , etc., depending on the location of the isotopic substitution relative to the reaction site. Secondary isotope effects result from a tightening or loosening of a C–H bond at the TS. The strength of the bond may change because of a hybridization change or a change in the extent of hyperconjugation, for example. If an sp^3 carbon is converted to sp^2 as reaction occurs, a hydrogen bound to the carbon will experience decreased resistance to C–H bending. The freeing of the vibration for a C–H bond is greater than that for a C–D bond because the former is slightly longer, and the vibration has a larger amplitude. This will result in a normal isotope effect. Entry 5 in Scheme 3.4 is an example of such a reaction that proceeds through a carbocation intermediate. An inverse isotope effect will occur if coordination at the reaction center increases in the TS. The bending vibration will become more restricted. Entry 4 in Scheme 3.4 exemplifies a case involving conversion of a tricoordinate carbonyl group to a tetravalent cyanohydrin. In this case the secondary isotope effect is 0.73.

Secondary isotope effects at the β -position have been especially thoroughly studied in nucleophilic substitution reactions. When carbocations are involved as intermediates, substantial β -isotope effects are observed because the hyperconjugative stabilization by the β -hydrogens weakens the C–H bond.¹²² The observed secondary isotope effects are normal, as would be predicted since the bond is weakened.



Detailed analysis of isotope effects reveals that there are many other factors that can contribute to the overall effect in addition to the dominant change in bond vibrations. There is not a sharp numerical division between primary and secondary effects,

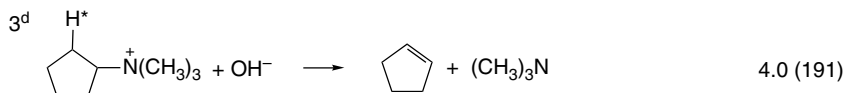
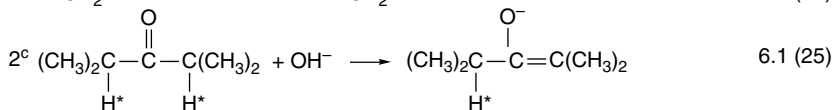
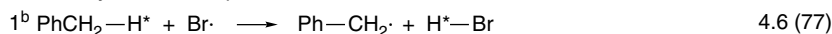
¹²¹. K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955); F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

¹²². V. J. Shiner, W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Am. Chem. Soc.*, **90**, 809 (1968); A. J. Kresge and R. J. Preto, *J. Am. Chem. Soc.*, **89**, 5510 (1967); G. J. Karabatsos, G. C. Sonnichsen, C. G. Papaioannou, S. E. Scheppele, and R. L. Shone, *J. Am. Chem. Soc.*, **89**, 463 (1967); D. D. Sunko and W. J. Hehre, *Prog. Phys. Org. Chem.*, **14**, 205 (1983).

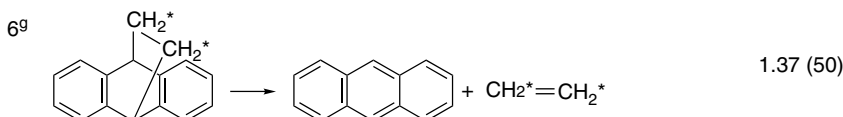
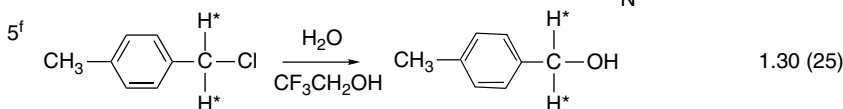
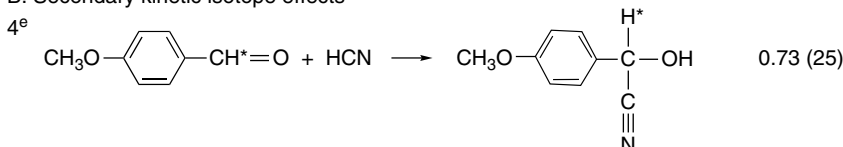
Reaction

 $k_H/k_D (^{\circ}\text{C})$

A. Primary kinetic isotope effects



B. Secondary kinetic isotope effects



a. Temperature of measurement is indicated in parentheses.

b. K. B. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.*, **80**, 3033 (1958).

c. R. A. Lynch, S. P. Vincenti, Y. T. Lin, L. D. Smucker, and S. C. Subba Rao, *J. Am. Chem. Soc.*, **94**, 8351 (1972).

d. W. H. Saunders, Jr., and T. A. Ashe, *J. Am. Chem. Soc.*, **91**, 473 (1969).

e. L. do Amaral, H. G. Bull, and E. H. Cordes, *J. Am. Chem. Soc.*, **94**, 7579 (1972).

f. V. J. Shiner, Jr., M. W. Rapp, and H. R. Pinnick, Jr., *J. Am. Chem. Soc.*, **92**, 232 (1970).

g. M. Taagepera and E. R. Thornton, *J. Am. Chem. Soc.*, **94**, 1168 (1972).

especially in the range between 1 and 2. For these reasons, isotope effects are usually used in conjunction with other criteria in the description of reaction mechanisms.¹²³

A new method for determining KIE using compounds of natural isotopic abundance has been developed.¹²⁴ This method makes experimental data more readily available. The method is based on the principle that as the reaction proceeds, the amount of the slower reacting isotope, e.g., ^2H or ^{13}C , is enriched in the remaining reactant. For example, an isotope effect of 1.05 leads to $\sim 25\%$ enrichment of the less reactive isotope at 99% conversion. The extent of enrichment can be measured by ^2H

^{123.} For more complete discussion of isotope effects see: W. H. Saunders, in *Investigation of Rates and Mechanisms of Reactions*, E. S. Lewis, ed., *Techniques of Organic Chemistry*, 3rd Edition, Vol. VI, Part 1, John Wiley & Sons, New York, 1974, pp. 211–255; L. Melander and W. H. Saunders, Jr., *Reaction Rates of Isotopic Molecules*, Wiley, New York, 1980; W. H. Saunders, in *Investigation of Rates and Mechanisms of Reactions*, C. F. Bernasconi, ed., *Techniques of Organic Chemistry*, 4th Edition, Vol. VI, Part 1, Interscience, New York, 1986, Chap. VIII.

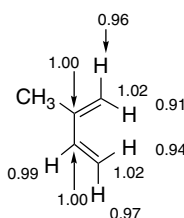
¹²⁴. D. A. Singleton and A. A. Thomas, *J. Am. Chem. Soc.*, **117**, 9357 (1995).

or ^{13}C NMR spectroscopy. The ratio of enrichment is related to the fraction of reaction completed and allows calculation of the KIE.

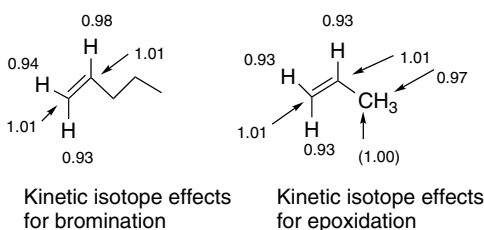
$$\text{KIE} = \frac{\ln(1 - F)}{\ln[(1 - F)R/R_0]} \quad (3.41)$$

where F is the fractional completion and R/R_0 is the isotopic enrichment.

The method can be simultaneously applied to each atom of interest. An atom that is expected to have a negligible KIE is selected as an internal standard. For example, with the methyl group as the internal standard, the KIE for every other position in isoprene was determined for the Diels-Alder reaction with maleic anhydride. This method is especially useful for the measurement of carbon isotope effects, where normal methods require synthesis of isotopic labeled reactants.



The experimental KIE can be compared with KIEs calculated from transition structures on the basis of the vibrational frequencies associated with specific bonds. This information is available from computed transition structures,¹²⁵ and the comparison can provide a direct experimental means of evaluating the computed transition structures.¹²⁶ The method has also been used to measure KIE in reactions such as the bromination of pentene¹²⁷ and epoxidation of propene.¹²⁸ Those transition structures that are inconsistent with the observed KIE can be excluded.



3.6. Linear Free-Energy Relationships for Substituent Effects

3.6.1. Numerical Expression of Linear Free-Energy Relationships

Many important relationships between substituent groups and chemical properties have been developed. For example, in Section 1.2.5 (p. 53), we discussed the effect

¹²⁵ M. Saunders, K. E. Laidig, and M. Wolfsberg, *J. Am. Chem. Soc.*, **111**, 8989 (1989).

¹²⁶ J. E. Baldwin, V. P. Reddy, B. A. Hess, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **110**, 8554 (1988); K. N. Houk, S. M. Gustafson, and K. A. Black, *J. Am. Chem. Soc.*, **114**, 8565 (1992); J. W. Storer, L. Raimondi, and K. N. Houk, *J. Am. Chem. Soc.*, **116**, 9675 (1994).

¹²⁷ S. R. Merrigan and D. A. Singleton, *Org. Lett.*, **1**, 327 (1997).

¹²⁸ D. A. Singleton, S. R. Merrigan, J. Liu, and K. N. Houk, *J. Am. Chem. Soc.*, **119**, 3385 (1997).

of substituent groups on the acid strength of acetic acid derivatives. It was noted in particular that the presence of groups more electronegative than hydrogen increases the acid strength relative to acetic acid. In Section 3.4, we dealt with substituent effects on carbocation, carbanion, radical, and carbonyl addition intermediates. In many cases, structure-reactivity relationships can be expressed quantitatively in ways that are useful both for interpretation of reaction mechanisms and for prediction of reaction rates and equilibria. The most widely applied of these relationships is the *Hammett equation*, which correlates rates and equilibria for many reactions of compounds containing substituted phenyl groups. It was noted in the 1930s that there is a linear relationship between the acid strengths of substituted benzoic acids and the rates of many other chemical reactions, e.g., the rates of hydrolysis of substituted ethyl benzoates. The correlation is illustrated graphically in Figure 3.25, which shows $\log k/k_0$, where k_0 is the rate constant for hydrolysis of ethyl benzoate and k is the rate constant for the substituted esters plotted against $\log K/K_0$, where K and K_0 are the corresponding acid dissociation constants.

Analogous plots for many other reactions of aromatic compounds show a similar linear correlation with the acid dissociation constants of the corresponding benzoic acids, but with a range of both positive and negative slopes. Neither the principles of thermodynamics nor transition state theory require that there be such linear relationships. In fact, many reaction series fail to show linear correlations. Insight into the significance of the correlations can be gained by considering the relationship between the correlation equation and the free-energy changes involved in the two processes. The line in Figure 3.25 defines an equation in which m is the slope of the line:

$$m \log \frac{K}{K_0} = \log \frac{k}{k_0} \quad (3.42)$$

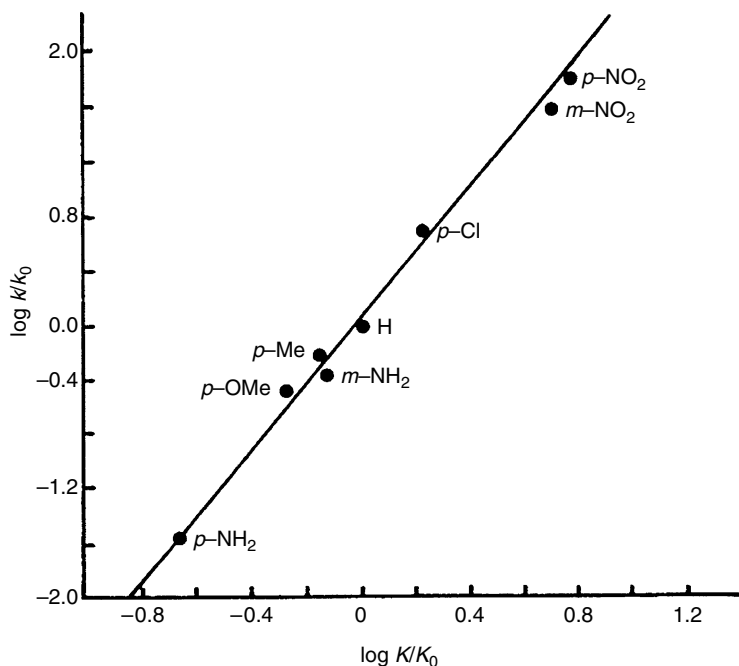


Fig. 3.25. Correlation of acid dissociation constants of benzoic acids with rates of basic hydrolysis of ethyl benzoates.

$$\begin{aligned}
 m(\log K - \log K_0) &= \log k - \log k_0 \\
 m(-\Delta G/2.3RT + \Delta G_0/2.3RT) &= \Delta G^\ddagger/2.3RT + \Delta G_0^\ddagger/2.3RT \\
 m(-\Delta G + \Delta G_0) &= -\Delta G^\ddagger + \Delta G_0^\ddagger \\
 m\Delta\Delta G &= \Delta\Delta G^\ddagger
 \end{aligned}
 \tag{3.43}$$

The linear correlation therefore indicates that the change in ΔG^\ddagger on introduction of a series of substituent groups is *directly proportional* to the change in the ΔG of ionization that is caused by the same series of substituents on benzoic acid. The correlations arising from such direct proportionality in free-energy changes are called *linear free-energy relationships*.¹²⁹

Since ΔG and ΔG^\ddagger are combinations of enthalpy and entropy terms, a linear free-energy relationship between two reaction series can result from one of three circumstances: (1) ΔH is constant and the ΔS terms are proportional for the series; (2) ΔS is constant and the ΔH terms are proportional; or (3) ΔH and ΔS are linearly related. Dissection of the free-energy changes into enthalpy and entropy components has often shown the third case to be true.

The Hammett linear free-energy relationship is expressed in the following equations for equilibria and rate data, respectively:

$$\log \frac{K}{K_0} = \sigma\rho \tag{3.44}$$

$$\log \frac{k}{k_0} = \sigma\rho \tag{3.45}$$

The numerical values of the terms σ and ρ are defined by selection of the reference reaction, the ionization of benzoic acids. This reaction is assigned the *reaction constant* $\rho = 1$. The *substituent constant*, σ , can then be determined for a series of substituent groups by measurement of the acid dissociation constant of the substituted benzoic acids. The σ values are then used in the correlation of other reaction series, and the ρ values of the reactions are thereby determined. The relationship between Equations (3.44) and (3.45) is evident when the Hammett equation is expressed in terms of free energy. For the standard reaction $\log[K/K_0] = \sigma\rho$:

$$-\Delta G/2.3RT + \Delta G_0/2.3RT = \sigma\rho = \sigma \tag{3.46}$$

since $\rho = 1$ for the standard reaction. Substituting into Eq. (3.42):

$$\begin{aligned}
 m\sigma &= -\Delta G^\ddagger/2.3RT + \Delta G_0^\ddagger/2.3RT \\
 m\sigma &= \log k - \log k_0 \\
 m\sigma &= \log \frac{k}{k_0}
 \end{aligned}
 \tag{3.47}$$

¹²⁹. A. Williams, *Free-Energy Relationships in Organic and Bio-Organic Chemistry*, Royal Society of Chemistry, Cambridge, UK, 2003.

The value of σ reflects the effect the substituent group has on the ΔG of ionization of the substituted benzoic acid, and several factors contribute. A substituent group can affect electron density on the benzene ring by both resonance and polar effects. These changes in charge distribution affect the relative energy of the reactant and product and cause a shift in the equilibrium for the reaction. In the case of a reaction rate, the relative effect on the reactant and the TS determine the change in ΔG^\ddagger .

The effect of substituents is illustrated in Figure 3.26. Because substituent effects are a combination of resonance and polar effects, individual substituents may have both electron-donating and electron-withdrawing components (see Scheme 3.1). For example, the methoxy group is a π donor but a σ acceptor. As resonance effects are generally dominant in aromatic systems, the overall effect of a methoxy group is electron release (in the *ortho* and *para* positions). For other groups, such as NO_2 and CN , the resonance and polar effects are reinforcing. The main polar effect seems to be electrostatic¹³⁰ (through space) and is sometimes referred to as a *field effect*, to distinguish it from an *inductive effect* (through bonds).

The Hammett equation in the form Equation (3.44) or (3.45) is free of complications owing to steric effects because it is applied only to *meta* and *para* substituents. The geometry of the benzene ring ensures that groups in these positions cannot interact sterically with the site of reaction. The σ values for many substituents have been determined, and some are shown in Table 3.26. Substituent constants are available for a much wider range of substituents.¹³¹ The σ value for any substituent reflects the interaction of the substituent with the reacting site by a combination of resonance and polar interactions. Table 3.26 lists some related substituent constants such as σ^+ , σ^- , σ_I , and σ_R . We discuss these shortly. Table 3.27 shows a number of ρ values. The ρ value reflects the sensitivity of the particular reaction to substituent effects. The examples that follow illustrate some of the ways in which the Hammett equation can be used.

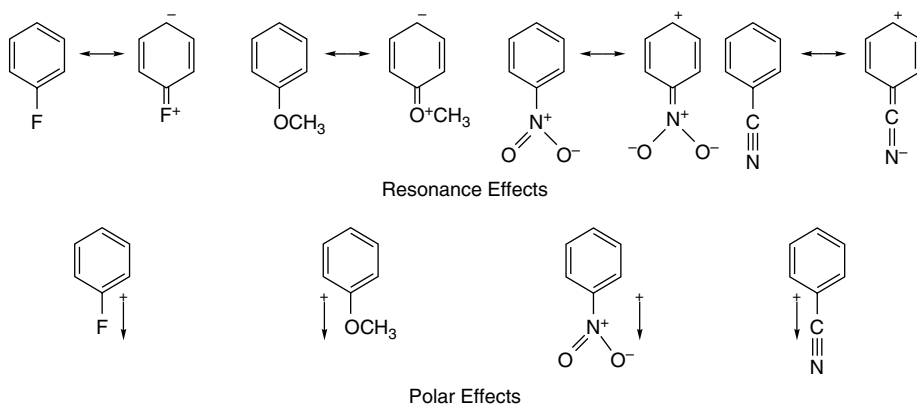


Fig. 3.26. Resonance and polar effects of representative substituents.

¹³⁰. K. Bowden and E. J. Grubbs, *Chem. Soc. Rev.*, **25**, 171 (1996).

¹³¹. C. Hansch, A. Leo, and R. W. Taft, *Chem. Rev.*, **91**, 165 (1991); J. Shorter, *Aust. J. Chem.*, **48**, 1453 (1995); J. Shorter, *Pure Appl. Chem.*, **66**, 2451 (1994); J. Shorter, *Aust. J. Chem.*, **51**, 525 (1988); J. Shorter, *Pure Appl. Chem.*, **69**, 2497 (1997).

Table 3.26. Substituent Constants^a

Substituent	Structure	σ_m	σ_p	σ^+	σ^-	σ_I	σ_R
Acetamido	CH ₃ CONH	0.21	0.00	-0.60	0.46	0.28	-0.35
Acetoxy	CH ₃ CO ₂	0.37	0.45	0.19		0.38	-0.23
Acetyl	CH ₃ CO	0.38	0.50		0.84	0.30	0.20
Amino	NH ₂	-0.16	-0.66	-1.30	-0.15	0.17	-0.80
Bromo	Br	0.37	0.23	0.15	0.25	0.47	-0.25
<i>t</i> -Butyl	(CH ₃) ₃ C	-0.10	-0.20	-0.26	-0.13	-0.01	-0.18
Carboxy	HO ₂ C	0.37	0.45	0.42	0.77	0.30	0.11
Chloro	Cl	0.37	0.23	0.11	0.19	0.47	-0.25
Cyano	N≡C	0.56	0.66	0.66	1.00	0.57	0.08
Diazonium	N ⁺ ≡N	1.76	1.91		3.43		
Dimethylamino	(CH ₃) ₂ N	-0.16	-0.83	-1.70	-0.12	0.13	-0.88
Ethoxy	C ₂ H ₅ O	0.10	-0.24	-0.81	-0.28	0.28	-0.57
Ethenyl	CH ₂ =CH	-0.06	0.04	-0.16		0.11	-0.15
Ethyl	C ₂ H ₅	-0.07	-0.15	-0.30	-0.19	-0.01	-0.14
Ethynyl	HC≡C	0.21	0.23	0.18	0.53	0.29	-0.04
Fluoro	F	0.34	0.06	-0.07	-0.03	0.54	-0.48
Hydrogen	H	0.0	0.0	0.0	0.0	0.0	0.0
Hydroxy	HO	0.12	-0.37	-0.92	-0.37	0.24	-0.62
Methanesulfonyl	CH ₃ SO ₂	0.60	0.72		1.13	0.59	0.11
Methoxy	CH ₃ O	0.12	-0.27	-0.78	-0.26	0.30	-0.58
Methoxycarbonyl	CH ₃ OCO	0.37	0.45	0.49	0.74	0.32	0.11
Methyl	CH ₃	-0.07	-0.17	-0.31	-0.17	-0.01	-0.16
Methylthio	CH ₃ S	0.15	0.00	-0.60	0.06	0.30	
Nitro	NO ₂	0.71	0.78	0.79	1.27	0.67	0.10
Phenyl	C ₆ H ₅	0.06	0.01	-0.18	0.02	0.12	-0.11
Trifluoromethyl	CF ₃	0.43	0.54	0.61	0.65	0.40	0.11
Trimethylammonio	(CH ₃) ₃ N ⁺	0.88	0.82	0.41	0.77	1.07	-0.11
Trimethylsilyl	(CH ₃) ₃ Si	-0.04	-0.07	0.02		-0.11	0.12

a. Values of σ_m , σ_p , σ^+ , and σ^- are from C. Hansch, A. Leo, and R. W. Taft, *Chem. Rev.*, **91**, 165 (1991); Values of σ_I and σ_R are from M. Charton, *Prog. Phys. Org. Chem.*, **13**, 119 (1981).

Example 3.2 The pK_a of *p*-chlorobenzoic acid is 3.98; that of benzoic acid is 4.19. Calculate σ for *p*-Cl.

$$\begin{aligned}
 \sigma &= \log \frac{K_{p\text{-Cl}}}{K_H} = \log K_{p\text{-Cl}} - \log K_H \\
 &= -\log K_H - (\log K_{p\text{-Cl}}) \\
 &= pK_{\sigma H} - pK_{\sigma p\text{-Cl}} \\
 &= 4.19 - 3.98 = 0.21
 \end{aligned}$$

Example 3.3 The ρ value for alkaline hydrolysis of methyl esters of substituted benzoic acids is 2.38, and the rate constant for hydrolysis of methyl benzoate under the conditions of interest is $2 \times 10^{-4} M^{-1} s^{-1}$. Calculate the rate constant for the hydrolysis of methyl *m*-nitrobenzoate.

$$\log \frac{k_{m\text{-NO}_2}}{k_H} = \sigma_{m\text{-NO}_2}(\rho) = (0.71)(2.38) = 1.69$$

Table 3.27. Reaction Constants^a

Reaction	ρ
$\text{ArCO}_2\text{H} \rightleftharpoons \text{ArCO}_2^- + \text{H}^+, \text{ water}$	1.00
$\text{ArCO}_2\text{H} \rightleftharpoons \text{ArCO}_2^- + \text{H}^+, \text{ ethanol}$	1.57
$\text{ArCH}_2\text{CO}_2\text{H} \rightleftharpoons \text{ArCH}_2\text{CO}_2^- + \text{H}^+, \text{ water}$	0.56
$\text{ArCH}_2\text{CH}_2\text{CO}_2\text{H} \rightleftharpoons \text{ArCH}_2\text{CH}_2\text{CO}_2^- + \text{H}^+, \text{ water}$	0.24
$\text{ArOH} \rightleftharpoons \text{ArO}^- + \text{H}^+, \text{ water}$	2.26
$\text{ArNH}_3^+ \rightleftharpoons \text{ArNH}_2 + \text{H}^+, \text{ water}$	3.19
$\text{ArCH}_2\text{NH}_3^+ \rightleftharpoons \text{ArCH}_2\text{NH}_2 + \text{H}^+, \text{ water}$	1.05
$\text{ArCO}_2\text{C}_2\text{H}_5 + ^-\text{OH} \longrightarrow \text{ArCO}_2^- + \text{C}_2\text{H}_5\text{OH}$	2.61
$\text{ArCH}_2\text{CO}_2\text{C}_2\text{H}_5 + ^-\text{OH} \longrightarrow \text{ArCH}_2\text{CO}_2^- + \text{C}_2\text{H}_5\text{OH}$	1.00
$\text{ArCH}_2\text{Cl} + \text{H}_2\text{O} \longrightarrow \text{ArCH}_2\text{OH} + \text{HCl}$	-1.31
$\text{ArC}(\text{CH}_3)_2\text{Cl} + \text{H}_2\text{O} \longrightarrow \text{ArC}(\text{CH}_3)_2\text{OH} + \text{HCl}$	-4.48
$\text{ArNH}_2 + \text{PhCOCl} \longrightarrow \text{ArNHCOPh} + \text{HCl}$	-3.21

a. From R. P. Wells, *Linear Free Energy Relationships*, Academic Press, New York, 1968, pp. 12-13.

$$\frac{k_{m-\text{NO}_2}}{k_{\text{H}}} = 49$$

$$k_{m-\text{NO}_2} = 98 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$$

Example 3.4 Using data in Tables 3.26 and 3.27, calculate how much faster than *p*-nitrobenzyl chloride *p*-bromobenzyl chloride will hydrolyze in water.

$$\log \frac{k_{\text{p-Br}}}{k_{\text{H}}} = (-1.31)(0.23), \quad \log \frac{k_{\text{p-NO}_2}}{k_{\text{H}}} = (-1.31)(0.78)$$

$$\log k_{\text{Br}} - \log k_{\text{H}} = 0.30, \quad \log k_{\text{NO}_2} - \log k_{\text{H}} = -1.02$$

$$\log k_{\text{Br}} + 0.30 = \log k_{\text{H}}, \quad \log k_{\text{NO}_2} + 1.02 = \log k_{\text{H}}$$

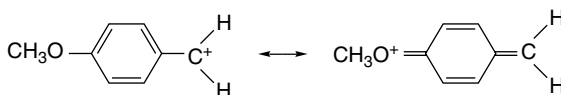
$$\log k_{\text{Br}} + 0.30 = \log k_{\text{NO}_2} + 1.02$$

$$\log k_{\text{Br}} - \log k_{\text{NO}_2} = 0.72$$

$$\log \frac{k_{\text{Br}}}{k_{\text{NO}_2}} = 0.72$$

$$\frac{k_{\text{Br}}}{k_{\text{NO}_2}} = 5.25$$

As we mentioned earlier, not all reaction series can be correlated by a Hammett equation. An underlying reason for the inability of Hammett σ_m and σ_p values to correlate all reaction series is that the substituent effects used to assign σ are a mixture of resonance and polar components. When direct resonance interaction with a reaction site is possible, the extent of the resonance increases and the substituent constants appropriate to the “normal” mix of resonance and polar effects fail. There have been various attempts to develop sets of σ values that take extra resonance interactions into account. In addition to the σ_m and σ_p values used with the classical Hammett equation Table 3.27 lists substituent constants σ^+ and σ^- . These are substituent constant sets that reflect enhanced resonance participation. The σ^+ values are used for reactions in which there is direct resonance interaction between an electron donor substituent and a cationic reaction center, whereas the σ^- set pertains to reactions in which there is a direct resonance interaction between an electron acceptor and an anionic reaction site. In these cases, the resonance component of the substituent effect is particularly important.



Direct resonance interaction with cationic center



Direct resonance interaction with anionic center

One approach to correct for the added resonance interaction is a modification of the Hammett equation known as the Yukawa-Tsuno equation¹³²:

$$\log \frac{k}{k_0} = \rho(\sigma^\circ + r\Delta\bar{\sigma}_{R^+}) \quad (3.48)$$

$$\text{where } \bar{\sigma}_{R^+} = \sigma^+ - \sigma^\circ$$

The additional parameter r is adjusted from reaction to reaction to optimize the correlation. It reflects the extent of the additional resonance contribution. A large r corresponds to a reaction with a large resonance component, whereas when r goes to zero, the equation is identical to the original Hammett equation. When there is direct conjugation with an electron-rich reaction center, an equation analogous to Equation (3.48) can be employed, but σ^- is used instead of σ^+ .

A more ambitious goal is to completely separate resonance and polar effects by using independent substituent constants to account for them. The resulting equation, called a *dual-substituent-parameter equation*, takes the form

$$\log \frac{K}{K_0} \quad \text{or} \quad \log \frac{k}{k_0} = \sigma_I \rho_I + \sigma_R \rho_R \quad (3.49)$$

where ρ_I and ρ_R are the reaction constants that reflect the sensitivity of the system to polar and resonance effects. The σ_I values have been defined from studies in reaction systems where no resonance component should be present.¹³³

¹³². Y. Tsuno and M. Fujio, *Chem. Soc. Rev.*, **25**, 129 (1996).

¹³³. M. Charton, *Prog. Phys. Org. Chem.*, **13**, 119 (1981).

In general, the dissection of substituent effects need not be limited to the resonance and polar components that are of special prominence in reactions of aromatic compounds. Any type of substituent interaction with a reaction center might be indicated by a substituent constant characteristic of the particular type of interaction and a reaction parameter indicating the sensitivity of the reaction series to that particular type of interaction. For example, it has been suggested that electronegativity and polarizability can be treated as substituent effects that are separate from polar and resonance effects.¹³⁴ This gives rise to the equation

$$\log \frac{k}{k_0} = \sigma_F \rho_F + \sigma_R \rho_R + \sigma_\chi \rho_\chi + \sigma_\alpha \rho_\alpha \quad (3.50)$$

where σ_F is the polar, σ_R is the resonance, σ_χ is the electronegativity, and σ_α is the polarizability substituent constant. In general, we emphasize the resonance and polar components in our discussion of substituent effects.

The Hammett substituent constants in Table 3.26 provide a more quantitative interpretation of substituent effects than was given in Scheme 3.1, where substituents were simply listed as EWG or ERG with respect to resonance and polar components. The values of σ_R and σ_I provide comparative evaluations of the separate resonance and polar effects. By comparing σ_R and σ_I , individual substituents can be separated into four quadrants, as in Scheme 3.5. Alkyl groups are electron releasing by both resonance and polar effects. Substituents such as alkoxy, hydroxy, and amino, which can act as resonance donors, have negative σ_p and σ^+ values, but when polar effects are dominant these substituents act as EWGs, as illustrated by the positive σ_m and σ_I values. A third group of substituents act as EWGs by both resonance and polar interactions. This group includes the carbonyl substituents, such as in aldehydes, ketones, esters, and amides, as well as cyano, nitro, and sulfonyl substituents. Of the common groups, only trialkylsilyl substituents are electron withdrawing by resonance and electron donating by polar effects, and both effects are weak.

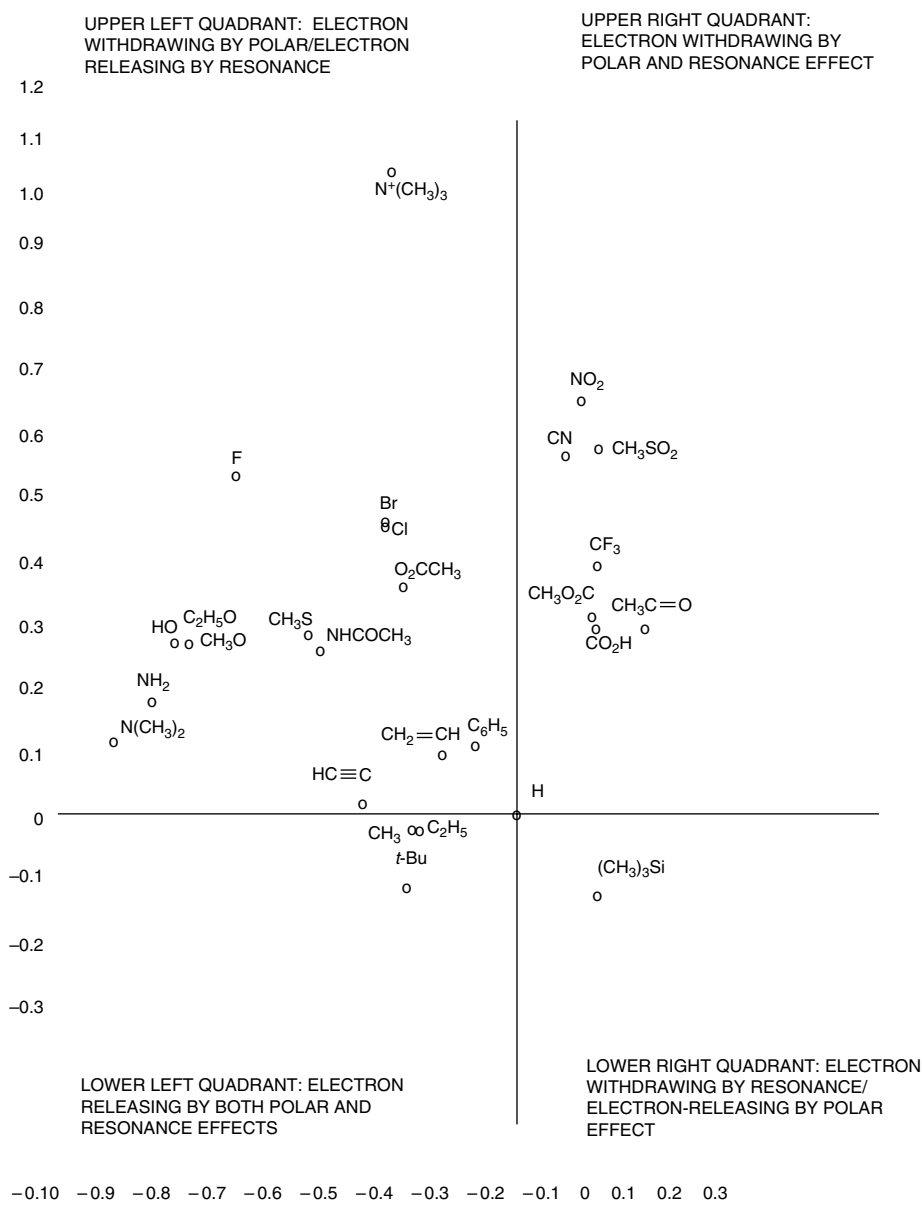
3.6.2. Application of Linear Free-Energy Relationships to Characterization of Reaction Mechanisms

Let us now consider how linear free-energy relationships can provide insight into reaction mechanisms. The choice of benzoic acid ionization as the reference reaction for the Hammett equation leads to $\sigma > 0$ for EWGs and $\sigma < 0$ for ERGs, since EWGs favor the ionization of the acid and ERGs have the opposite effect. Further inspection of the Hammett equation shows that ρ will be positive for all reactions that are favored by ERGs and negative for all reactions that are favored by EWGs. If the rates of a reaction series show a satisfactory correlation, both the sign and magnitude of ρ provide information about the TSs and intermediates for the reaction. In Example 3.3 (p. 340), the ρ value for hydrolysis of substituted methyl benzoates is +2.38. This indicates that EWGs facilitate the reaction and that the reaction is *more sensitive* ($\rho > 1$) to substituent effects than the ionization of benzoic acids. The observation that the reaction is favored by EWGs is in agreement with the mechanism for ester hydrolysis discussed in Section 3.4.4. The tetrahedral intermediate is negatively charged. Its formation should therefore be favored by substituents that stabilize the developing charge. There is also a ground state effect working in the same direction. EWG substituents make

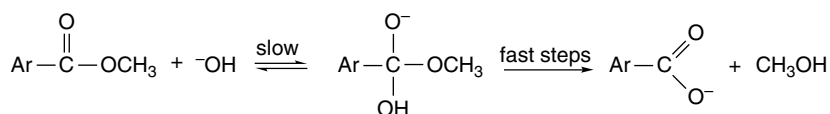
¹³⁴ R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, **16**, 1 (1987).

Scheme 3.5. Relationship between σ_I and σ_R Substituent Constants

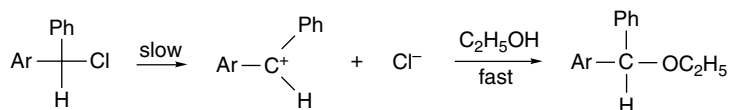
SECTION 3.6

*Linear Free-Energy
Relationships for
Substituent Effects*

the carbonyl group more electrophilic and favor the addition of hydroxide ion in the rate-determining step.



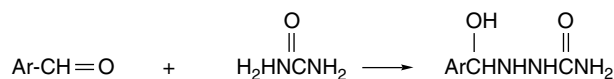
The solvolysis of diarylmethyl chlorides in ethanol correlates with σ^+ and shows a ρ value of -4.2 , indicating that ERGs strongly facilitate the reaction.¹³⁵ This ρ value is consistent with a mechanism involving carbocation formation as the rate-determining step. ERGs facilitate the ionization by a stabilizing interaction with the electron-deficient carbocation that develops as ionization proceeds.



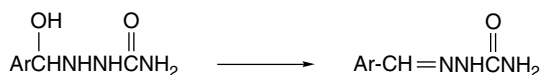
The large ρ shows that the reaction is very sensitive to substituent effects and implies that there is a relatively large redistribution of charge in going to the TS.

The magnitudes of substituent effects differ in solution and the gas phase. In general, substituent effects are much stronger in the latter because there is no “leveling effect” from solvation. For example, in the ionization of benzoic acids, the substituent effects in terms of ΔH are about 11 times larger in the gas phase than in the aqueous phase.¹³⁴ The relative importance of direct resonance interactions seems to be greater in aqueous solution. For example, the ρ_p value of NH_2 increases from -0.17 in the gas phase to -0.39 in benzene and -0.66 in water. This indicates that the charge separation implied by the resonance structures is facilitated by solvation.

Not all reactions can be described by the Hammett equations or the multiparameter variants. There can be several reasons for this. One possibility is a change in mechanism as substituents vary. In a multistep reaction, for example, one step may be rate determining for EWGs, but a different step may become rate limiting for ERG substituents. The rate of semicarbazone formation of benzaldehydes, for example, shows a nonlinear Hammett plot with ρ of about 3.5 for ERGs, but ρ near -0.25 for EWGs.¹³⁶ The change in ρ is believed to be the result of a change in the rate-limiting step.



rate-controlling step for electron-releasing substituents



rate-controlling step for electron-withdrawing substituents

Any reaction that undergoes a major change in mechanism or TS structure over the substituent series would be expected to give a nonlinear Hammett plot.

The development of linear free-energy relationships in aliphatic molecules is complicated because steric and conformation factors come into play along with electronic effects. A number of successful treatments of aliphatic systems have been developed by separating electronic effects from steric effects. We do not discuss these methods in the present work, but there are reviews available that can be consulted for information about this area.¹³⁷

¹³⁵ S. Nishida, *J. Org. Chem.*, **32**, 2692 (1967).

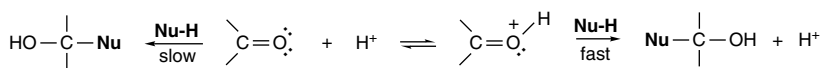
¹³⁶ D. S. Noyce, A. T. Bottini and S. G. Smith, *J. Org. Chem.*, **23**, 752 (1958).

¹³⁷ M. Charton, *Prog. Phys. Org. Chem.*, **10**, 81 (1973); S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).

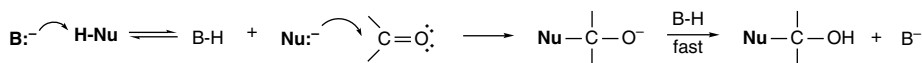
Many chemical reactions involve a *catalyst*. A very general definition of a catalyst is *a substance that makes a reaction path available with a lower energy of activation*. Strictly speaking, a catalyst is not consumed by the reaction, but organic chemists frequently speak of acid-catalyzed or base-catalyzed mechanisms that do lead to overall consumption of the acid or base. Better phrases under these circumstances would be *acid promoted* or *base promoted*. Catalysts can also be described as electrophilic or nucleophilic, depending on the catalyst's electronic nature. Catalysis by Lewis acids and Lewis bases can be classified as electrophilic and nucleophilic, respectively. In free-radical reactions, the *initiator* often plays a key role. An initiator is a substance that can easily generate radical intermediates. Radical reactions often occur by chain mechanisms, and the role of the initiator is to provide the free radicals that start the chain reaction. In this section we discuss some fundamental examples of catalysis with emphasis on proton transfer (Brønsted acid/base) and Lewis acid catalysis.

3.7.1. Catalysis by Acids and Bases

A detailed understanding of reaction mechanisms requires knowledge of the role catalysts play in the reaction. Catalysts do not affect the position of equilibrium of a reaction, which is determined by ΔG° and is independent of the path (mechanism) of the transformation. Catalysts function by increasing the rate of one or more steps in the reaction mechanism by providing a reaction path having a lower E_a . The most general family of catalytic processes are those that involve transfer of a proton. Many reactions are strongly catalyzed by proton donors (Brønsted acids) or proton acceptors (Brønsted bases). Catalysis occurs when the conjugate acid or conjugate base of the reactant is more reactive than the neutral species. As we discussed briefly in Section 3.4.4, reactions involving nucleophilic attack at carbonyl groups are often accelerated by acids or bases. Acid catalysis occurs when the conjugate acid of the carbonyl compound, which is much more electrophilic than the neutral molecule, is the kinetically dominant reactant. Base-catalyzed additions occur as a result of deprotonation of the nucleophile, generating a more reactive anion.

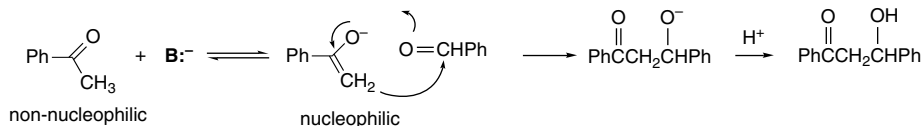


acid catalysis of carbonyl addition by reactant protonation



base catalysis of carbonyl addition by deprotonation of the nucleophile

Many important organic reactions involve carbanions as nucleophiles. The properties of carbanions were introduced in Section 3.4.2, and their reactivity is discussed in more detail in Chapter 6. Most C–H bonds are very weakly acidic and have no tendency to ionize spontaneously to form carbanions. Reactions that involve carbanion intermediates are therefore usually carried out in the presence of a base that can generate the reactive carbanion intermediate. Base-catalyzed addition reactions of carbonyl compounds provide many examples of this type of reaction. The reaction



3.7.1.1. Specific and General Acid/Base Catalysis. The effect that acid and base catalysts have on reaction rates can be quantitatively studied by kinetic techniques. It is possible to recognize two distinct types of catalysis by acids and bases. The term *specific acid catalysis* is used when the reaction rate is dependent on the *equilibrium protonation* of a reactant. This type of catalysis is independent of the structure of the various proton donors present in solution. Specific acid catalysis is governed by the *hydrogen ion concentration* (pH) of the solution. For example, for a reaction in a series of aqueous buffer systems, the rate of the reaction is a function of the pH, but not of the concentration or identity of the acidic and basic components of the buffers. The kinetic expression for such a reaction includes a term for hydrogen ion concentration, $[H^+]$, but not for any other proton donor. In *general acid catalysis* the nature and concentration of proton donors present in solution affect the reaction rate. The kinetic expression for such reactions include terms for each of the proton donors. The terms *specific base catalysis* and *general base catalysis* apply in the same way to base-catalyzed reactions.

SPECIFIC ACID CATALYSIS:

$$\text{Rate} = k[\text{H}^+][\text{X}][\text{Y}]$$

where $[X][Y]$ are the concentration of the reactants.

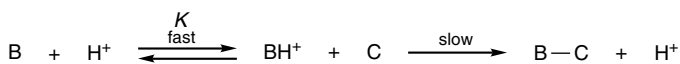
GENERAL ACID CATALYSIS:

$$\text{Rate} = k_1[\text{H}^+][\text{X}][\text{Y}] + k_2[\text{HA}^2][\text{X}][\text{Y}] + k_3[\text{HA}^3][\text{X}][\text{Y}] + \cdots + k_n[\text{HA}^n][\text{X}][\text{Y}]$$

where $\text{HA}^2, \text{HA}^3, \dots, \text{HA}^n$ are all kinetically significant proton donors.

The experimental detection of general acid catalysis is done by rate measurements at constant pH but differing buffer concentration or composition. The observation of a change in rate is evidence of general acid catalysis. If the rate remains constant, the reaction is dependent only on $[H^+]$ and exhibits specific acid catalysis. Similarly, reactions that are general base catalyzed show a dependence of the rate on the concentration and identity of the basic constituents of the buffer system.

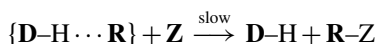
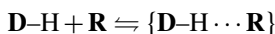
Specific acid catalysis is observed when a reaction proceeds through a protonated intermediate that is in equilibrium with its conjugate base. Since the position of this equilibrium is a function of the concentration of solvated protons, only a single acid-dependent term appears in the kinetic expression. For example, in a two-step reaction involving a rate-determining reaction of one reactant with the conjugate acid of a second, the kinetic expression is



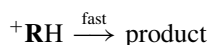
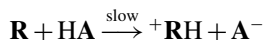
$$\text{Rate} = k_2[\text{BH}^+][\text{C}] = k_2[\text{C}]K[\text{B}][\text{H}^+] = k_{\text{obs}}[\text{H}^+][\text{B}][\text{C}]$$

In the actual experiments, since buffers are used to control pH, the points are extrapolated to zero buffer concentration by making measurements at several buffer concentrations (but at the same pH). Such plots are linear if the reaction is subject to specific acid base catalysis.

Several situations can lead to the observation of general acid catalysis. General acid catalysis can occur as a result of hydrogen bonding between the reactant **R** and a proton donor **D-H** to form a reactive complex $\{\text{D-H} \cdots \text{R}\}$, which then undergoes reaction with a reactant **Z**:

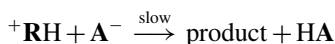
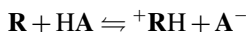


Under these circumstances, a distinct contribution to the overall rate is found for each potential hydrogen bond donor **D-H**. General acid catalysis is also observed when a rate-determining proton transfer occurs from acids other than the solvated proton:



Each acid HA^1 , HA^2 , etc., makes a contribution to the overall rate of the reaction.

General acid catalysis is also observed if a prior equilibrium between the reactant and the acid is followed by rate-controlling proton transfer. Each individual conjugate base A^- appears in the overall rate expression:



Note that specific acid catalysis describes a situation where the reactant is in *equilibrium* with regard to proton transfer and proton transfer is not rate-determining. On the other hand, each case that leads to general acid catalysis *involves proton transfer in the rate-determining step*. Because of these differences, the study of rates as a function of pH and buffer concentrations can permit conclusions about the nature of proton transfer processes and their relationship to the rate-determining step in a reaction.

The details of proton transfer processes can also be probed by examination of *solvent isotope effects* by comparing the rates of a reaction in H_2O versus D_2O . The solvent isotope effect can be either normal or inverse, depending on the nature of the proton transfer process. D_3O^+ is a stronger acid than H_3O^+ . As a result, reactants in D_2O solution are somewhat more extensively protonated than in H_2O at identical acid concentrations. A reaction that involves a rapid equilibrium protonation proceeds *faster* in D_2O than in H_2O because of the higher concentration of the protonated reactant. On the other hand, if proton transfer is part of the rate-determining step, the reaction will be *faster* in H_2O than in D_2O because of the normal primary kinetic isotope effect of the type of reaction.

3.7.1.2. *Brønsted Catalysis Law.* As might be expected, there is a relationship between the effectiveness of general acid catalysts and the acidic strength of a proton donor, as measured by its acid dissociation constant K_a . The stronger acids are more effective catalysts. This relationship is expressed by the *Brønsted catalysis law*:

$$\log k_{\text{cat}} = \alpha \log K + b \quad (3.51)$$

An analogous equation holds for catalysis by bases. This equation requires that the E_a for the catalytic step for a series of acids be directly proportional to ΔG of dissociation for the same series of acids. The proportionality constant α is an indication of the sensitivity of the catalytic step to structural changes, relative to the effect of the same structural changes on acid dissociation. It is often found that a single proportionality constant α is restricted to only structurally similar acids and that linear relationships having α values of different magnitude apply to each type of acid.

Figure 3.27 is plot of the Brønsted relationship for hydrolysis of a vinyl ether. The plot shows that the effectiveness of the various carboxylic acids as catalysts is related to their dissociation constants. In this particular case, the value of α is 0.79.¹³⁸

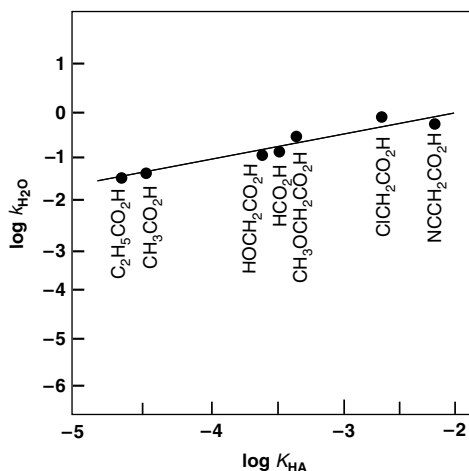
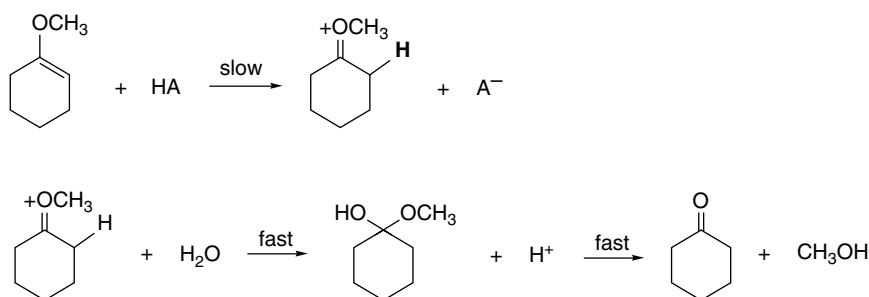


Fig. 3.27. Brønsted relation for the hydrolysis of cyclohexenyl methyl ether. Adapted from *J. Am. Chem. Soc.*, **93**, 413 (1971), by permission of the American Chemical Society.

¹³⁸ A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Am. Chem. Soc.*, **93**, 413 (1971).

Since α relates the sensitivity of the proton transfer process to that of dissociation of the acid, it is sometimes suggested that the value of α can be used as an indicator of TS structure. The closer α approaches unity, the greater the degree of proton transfer in the TS. There are limits to the generality of this interpretation, however.¹³⁹

3.7.1.3. Acidity Functions. Some organic reactions require acid concentrations considerably higher than can be accurately measured on the pH scale, which applies to relatively dilute aqueous solutions. For example, concentrated acidic solutions can have formal proton concentrations of 10M or more, but these formal concentrations are not a suitable measure of the *activity* of protons in such solutions. For this reason, *acidity functions* have been developed to measure the proton-donating strength of concentrated acidic solutions. The activity of the hydrogen ion (solvated proton) can be related to the extent of protonation of a series of bases by the equilibrium expression for the protonation reaction:

$$\begin{aligned} \text{B} + \text{H}^+ &\rightleftharpoons \text{B}^+\text{H} \\ K &= \frac{(\alpha_{\text{BH}^+})}{(\alpha_{\text{H}^+})(\alpha_{\text{B}})} = \frac{[\text{BH}^+] \gamma_{\text{BH}^+}}{(\alpha_{\text{H}^+}) + [\text{B}] \gamma_{\text{B}}} \end{aligned} \quad (3.52)$$

where γ is the activity coefficient for the base and its conjugate acid. A common measure of acidity is referred to as h_0 and is defined by measuring the extent of protonation of a series of bases for which K is measured. The relative concentration of the base and its conjugate acid then defines h_0 for any particular acidic solution:

$$h_0 = \frac{[\text{BH}^+] \gamma_{\text{BH}^+}}{K[\text{B}] \gamma_{\text{B}}} \quad (3.53)$$

The quantity H_0 defined as $-\log h_0$ is commonly tabulated and it corresponds to the pH of very concentrated acidic solutions. The H_0 values are established by making measurements in increasingly acidic solutions with a series of successively weaker bases. The series is begun by measuring a reference base in aqueous solution where $H_0 \sim \text{pH}$. This base can then be used to find the H_0 of a somewhat more acidic solution. The K of a somewhat weaker base is then determined in the more acidic solution. This second base can then be used to extend H_0 into a still more acidic solution. The process is continued by using a series of bases to establish H_0 for successively more acidic solutions.¹⁴⁰ The assumption involved in this procedure is that the ratio of the activity coefficients for the series of base cations does not change from solvent to solvent, that is,

$$\frac{\gamma_{\text{B}_1} [\text{H}^+]}{\gamma_{\text{B}_1}} = \frac{\gamma_{\text{B}_2} [\text{H}^+]}{\gamma_{\text{B}_2}} = \frac{\gamma_{\text{B}_3} [\text{H}^+]}{\gamma_{\text{B}_3}} = \dots \quad (3.54)$$

¹³⁹. A. J. Kresge, *J. Am. Chem. Soc.*, **92**, 3210 (1970); R. A. Marcus, *J. Am. Chem. Soc.*, **91**, 7224 (1969); F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.*, **94**, 3907 (1972); D. A. Jencks and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 7948 (1977); A. Pross, *J. Org. Chem.*, **49**, 1811 (1984).

¹⁴⁰. For reviews and discussion of acidity functions, see E. M. Arnett, *Prog. Phys. Org. Chem.*, **1**, 223 (1963); C. H. Rochester, *Acidity Functions*, Academic Press, New York, 1970; R. A. Cox and K. Yates, *Can. J. Chem.*, **61**, 225 (1983); C. D. Johnson and B. Stratton, *J. Org. Chem.*, **51**, 4100 (1986).

Table 3.28. H_0 as a Function of Composition of Aqueous Sulfuric Acid^a

% H ₂ SO ₄	H_0	% H ₂ SO ₄	H_0
5	0.24	55	-3.91
10	-0.31	60	-4.46
15	-0.66	65	-5.04
20	-1.01	70	-5.80
25	-1.37	75	-6.56
30	-1.72	80	-7.34
35	-2.06	85	-8.14
40	-2.41	90	-8.92
45	-2.85	95	-9.85
50	-3.38	98	-10.41

a. From J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).

Not surprisingly, the results often reveal a dependence on the particular type of base used, so no universal H_0 scale can be established. Nevertheless, this technique provides a very useful measure of the relative hydrogen ion activity of concentrated acid solutions that can be used in the study of reactions that proceed only at high acid concentrations. Table 3.28 gives H_0 values for some water-sulfuric acid mixtures.

3.7.1.4. pH-Rate Profiles. pH-Rate profiles are a useful tool for analysis of acid and base catalysis.¹⁴¹ The rate of the reaction is measured as a function of the pH. Reactions are typically studied under pseudo-first-order conditions so that the rates are first order in the reactant at each pH:

$$\text{Rate} = k_{\text{obs}}[\text{R}]$$

Observed pH rate profiles typically consist of several regions including segments with linear dependence on $[\text{H}^+]$ or $[\text{OH}^-]$, pH-independent, and curved transitions between linear areas. The occurrence of $[\text{H}^+]$ (or $[\text{OH}^-]$) in the rate expression indicates either that a protonated (or deprotonated) form of the reactant is involved (preequilibrium) or that H^+ (or OH^-) is involved in the rate-determining step. Figure 3.28 shows some pH dependencies that may be components of a specific profile. Curves (a) and (b) show linear dependence on $[\text{H}^+]$ and $[\text{OH}^-]$ that is due to specific acid and base catalysis, respectively. The horizontal portion of the profile corresponds to a reaction that does not involve acid or base catalysis. Usually the slope of the linear part of the curve is $-1(\text{H}^+)$ or $+1(\text{OH}^-)$ because there is only one protonation (or deprotonation) step.

The rate expressions for (a) and (b), respectively, would be:

$$(a) \text{ Rate} = k_{\text{H}^+}[\text{R}][\text{H}^+] + k_{\text{H}_2\text{O}}[\text{R}]$$

$$(b) \text{ Rate} = k_{\text{OH}^-}[\text{R}][\text{OH}^-] + k_{\text{H}_2\text{O}}[\text{R}]$$

where k_{H^+} , k_{OH^-} , and $k_{\text{H}_2\text{O}}$ are the rate constants for the acid-catalyzed, base-catalyzed, and uncatalyzed reactions, respectively.

For cases (c) and (d), the rates level off at high $[\text{H}^+]$ and $[\text{OH}^-]$, respectively. This circumstance occurs if the reactant is completely protonated (or deprotonated) so

¹⁴¹ J. M. Loudon, *J. Chem. Educ.*, **68**, 973 (1991).

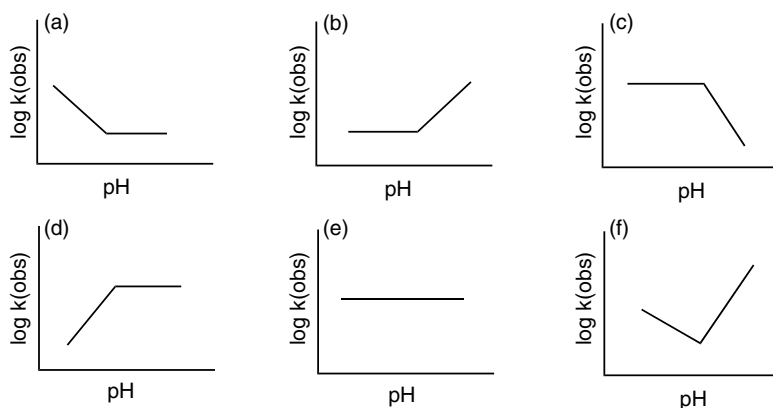


Fig. 3.28. Schematic components of pH rate profiles: (a) acid catalyzed with uncatalyzed component, (b) base catalyzed with uncatalyzed component, (c) acid catalyzed with saturation, (d) base catalyzed with saturation, (e) uncatalyzed reaction, (f) reaction subjected to both acid and base catalysis. Adapted from *J. Chem. Soc., Perkin Trans., 2*, 365 (2000).

that further increase in $[H^+]$ or $[OH^-]$ causes no further change in the rate. The form of the corresponding rate equations is

$$k_{\text{obs}} = \frac{K_{H^+}[H^+]K_a}{K_a + [H^+]} \quad (3.55)$$

where K_a is the acid dissociation constant of R.

For base catalysis with saturation, the form is

$$k_{\text{obs}} = \frac{k_{-OH}K_w}{K_a + [H^+]} \quad (3.56)$$

The curve in (f) would be observed for a reaction that is catalyzed by both acid and base, for which the rate expression is

$$\text{Rate} = k_{H^+}[H^+][R] + k_{-OH}[OH^-][R] + k_{H_2O}[R] \quad (3.57)$$

In general, there may be a change in mechanism or a change in the rate-limiting step across the range of pH. This results in a pH-rate profile that combines components from the profiles in (a)–(e) of Figure 3.28. There are useful conclusions that can be drawn by inspection of pH profiles. (1) The number of terms in the overall rate expression is one more than the number of upward bends in the profile. (2) upward bends signal a transition to a different mechanism. Each upward bend represents a new mechanism becoming a significant component of the total reaction. For example, in the case of a reaction catalyzed by both acid and base (and also involving an uncatalyzed component), the upward bend in the acidic region corresponds to the acid-catalyzed component and the upward bend in the basic region is the base-catalyzed component, as illustrated in Figure 3.29.

$$k_{\text{obs}} = k_{H^+}[H^+] + k_{-OH}[OH^-] + k_{H_2O} = k_{H^+}[H^+] + k_{-OH}\frac{K_w}{[H^+]} + k_{H_2O} \quad (3.58)$$

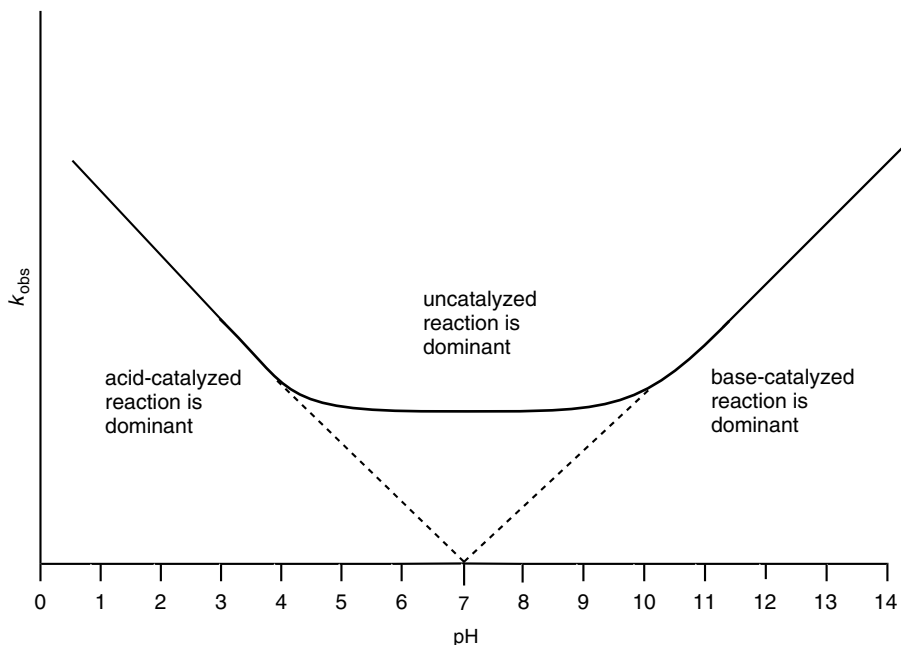
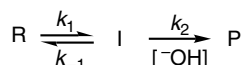
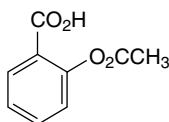


Fig. 3.29. pH-rate profile showing upward bends corresponding to the change from uncatalyzed to acid-catalyzed and base-catalyzed mechanisms.

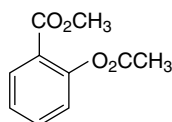
Downward bends in pH profiles occur when there is a change in the rate-limiting step. For example, if there is an unfavorable equilibrium between the reactant and an unstable intermediate, which then undergoes a base-catalyzed reaction, there will be a downward bend. The rate of the equilibrium is pH independent. At low $[\text{OH}^-]$, the rate-limiting step will be governed by k_2 . The rate will increase as $[\text{OH}^-]$ increases until it is no longer rate limiting. At that point k_1 becomes the rate-limiting step, $[\text{OH}^-]$ no longer affects the observed rate, and the curve bends downward:



We can illustrate the interpretation of pH rate profiles by considering the pH rate profile for the hydrolysis of aspirin. The pH rate profile and that of its methyl ester are shown in Figure 3.30. The methyl ester is a classic case in which there are both acid- and base-catalyzed regions and an uncatalyzed region as described by Equation (3.58). These features are characteristic of the normal ester hydrolysis mechanism outlined on pp. 325–326. Under the reaction conditions, only the more reactive *O*-aryl ester group is hydrolyzed. Aspirin, however, shows a region between pH 2 and pH 9 that reveals one downward and two upward bends. Thus there must be a fourth variant of the mechanism (since there are a total of three upward bends).



aspirin



aspirin methyl ester

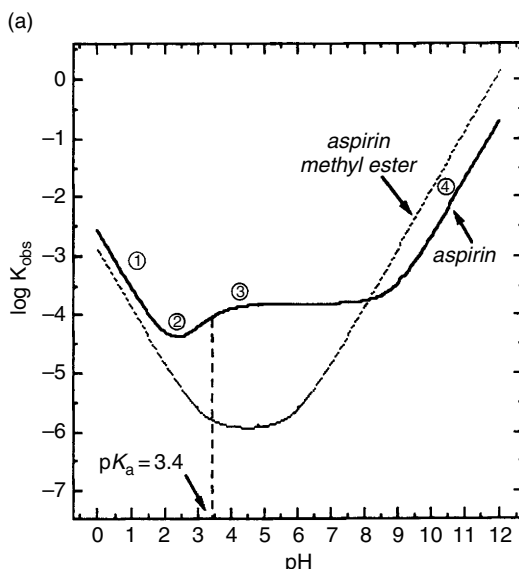
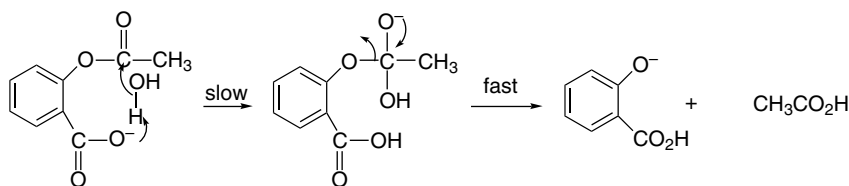


Fig. 3.30. pH rate profile of aspirin and its methyl ester. Reproduced from *J. Chem. Educ.*, **68**, 973 (1991).

The fact that there is a downward bend in the curve at about pH 5 suggests that the CO_2^- group in aspirin, which is absent from the methyl ester, might be involved in the reaction. The CO_2^- group becomes protonated in this region, which might account for the decreased rate below pH 5. This would require the addition of a fourth term to the rate curve where $[\text{As}^-]$ is the carboxylate anion of aspirin. The concentration of $[\text{As}^-]$ is governed by the acid dissociation constant K_{as} . This leads to the expression

$$k_{\text{obs}} = k_{\text{H}^+} [\text{H}^+] + \frac{k_{\text{H}_2\text{O}} [\text{H}^+]}{K_{\text{as}} + [\text{H}^+]} + \frac{k_i K_{\text{as}}}{K_{\text{as}} + [\text{H}^+]} + \frac{k_{-\text{OH}} K_{\text{w}}}{[\text{H}^+]}$$

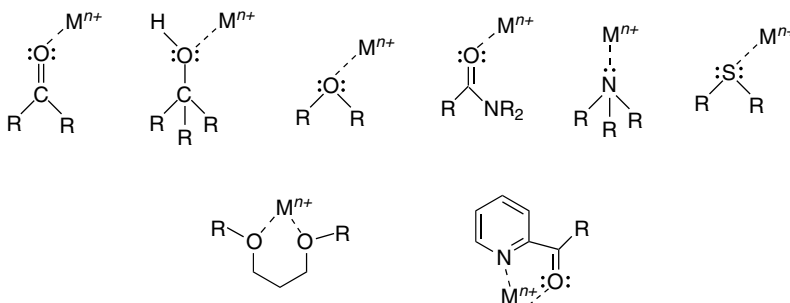
In the region pH 5 to pH 8 $[\text{As}^-]$ is constant, since it is completely deprotonated above pH 5, and the rate is pH independent in this region. Thus the pH-rate profile for aspirin identifies four distinct regions as the pH increases. Regions 1 and 4 correspond to reactions involving a H^+ and ^-OH in the rate-determining transition state and are the normal acid- and base-catalyzed mechanisms for ester hydrolysis. Region 2 corresponds to the uncatalyzed reaction and Region 3 is the fourth mechanism, which involves the anion of aspirin or a kinetically equivalent species. Based on other studies, this mechanism has been interpreted as a carboxylate-assisted deprotonation of water leading to rate-determining formation of the tetrahedral intermediate.¹⁴² (See Section 7.5 for discussion of the evidence for this mechanism.)



¹⁴². A. P. Fresht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 4857 (1967).

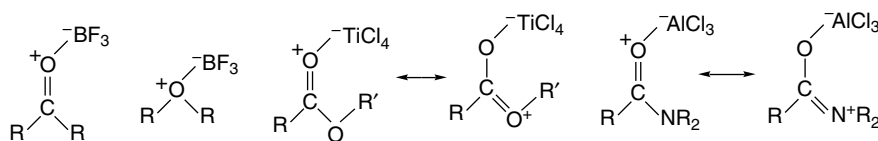
Lewis acids act as electron pair acceptors. The proton is an important special case, but many other compounds catalyze organic reactions by acting as electron pair acceptors. The most important Lewis acids in organic reactions are metal cations and covalent compounds of metals. Metal cations that function as Lewis acids include the alkali metal monocations Li^+ , Na^+ , K^+ , di- and trivalent ions such as Mg^{2+} , Ca^{2+} , Zn^{2+} , Sc^{3+} , and Bi^{3+} ; transition metal cations and complexes; and lanthanide cations, such as Ce^{3+} and Yb^{3+} . Neutral electrophilic covalent molecules can also act as Lewis acids. The most commonly employed of the covalent compounds include boron trifluoride, aluminum trichloride, titanium tetrachloride, and tin(IV)tetrachloride. Various other derivatives of boron, aluminum, titanium, and tin also are Lewis acid catalysts.

The catalytic activity of metal cations originates in the formation of a donor-acceptor complex between the cation and the reactant, which acts as a Lewis base. As a result of the complexation, the donor atom becomes effectively more electronegative. All functional groups that have unshared electron pairs are potential electron donors, but especially prominent in reaction chemistry are carbonyl oxygens (sp^2), hydroxy or ether (sp^3) oxygen, as well as similar nitrogen- and sulfur-containing functional groups. For oxygen and nitrogen functional groups, the catalysis generally correlates with hardness, so the smaller and more positively charged ions have the strongest effects. Halogen substituents can act as electron donors to strong Lewis acids. The presence of two potential donor atoms in a favorable geometric relationship permits formation of “bidentate” chelate structures and may lead to particularly strong complexes.



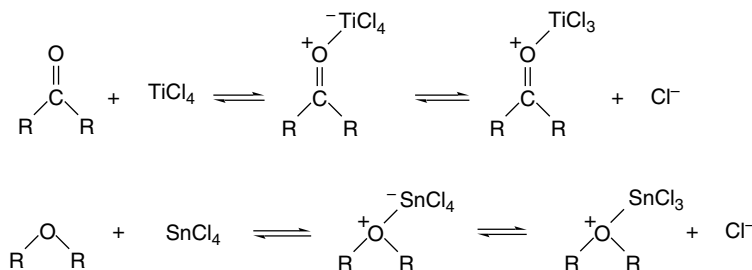
There is a partial transfer of charge to the metal ion from the donor atom, which increases the effective electronegativity of the donor atom. The Lewis acid complexes of carbonyl groups, for example, are more reactive to nucleophilic attack. Hydroxy groups complexed to metal cations are stronger acids and better leaving groups than an uncomplexed hydroxy. Ether or sulfide groups complexed with metal ions are better leaving groups.

Neutral compounds such as boron trifluoride and aluminum trichloride form Lewis acid-base complexes by accepting an electron pair from the donor molecule. The same functional groups that act as electron pair donors to metal cations can form complexes with boron trifluoride, aluminum trichloride, titanium tetrachloride, and related compounds. In this case the complex is formed between two neutral species, it too is neutral, but there is a formal positive charge on the donor atom and a formal negative charge on the acceptor atom.



Complexes of carbonyl oxygen with trivalent boron and aluminum compounds tend to adopt a geometry consistent with directional interaction with one of the oxygen lone pairs. Thus the C–O–M bonds tend to be in the trigonal (120° – 140°) range and the boron or aluminum is usually close to the carbonyl plane.¹⁴³ The structural specificity that is built into Lewis acid complexes can be used to advantage to achieve stereoselectivity in catalysis. For example, use of chiral ligands in conjunction with Lewis acids is frequently the basis for enantioselective catalysts.

Titanium(IV) tetrachloride and tin(IV) tetrachloride can form complexes that are similar to those formed by metal ions and those formed by neutral Lewis acids. Complexation can occur with displacement of a chloride from the metal coordination sphere or by an increase in the coordination number at the Lewis acid.



For example, the crystal structure of the adduct of titanium tetrachloride and the ester formed from ethyl 2-hydroxypropanoate (ethyl lactate) and acrylic acid has been determined.¹⁴⁴ It is a chelate with the oxygen donor atoms incorporated into the titanium coordination sphere along with the four chloride anions, as shown in Figure 3.31.

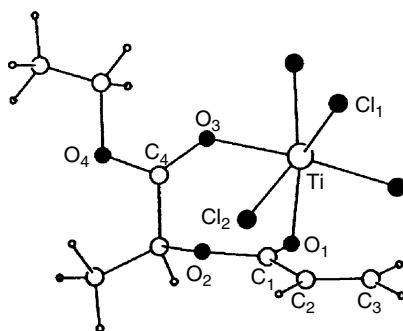
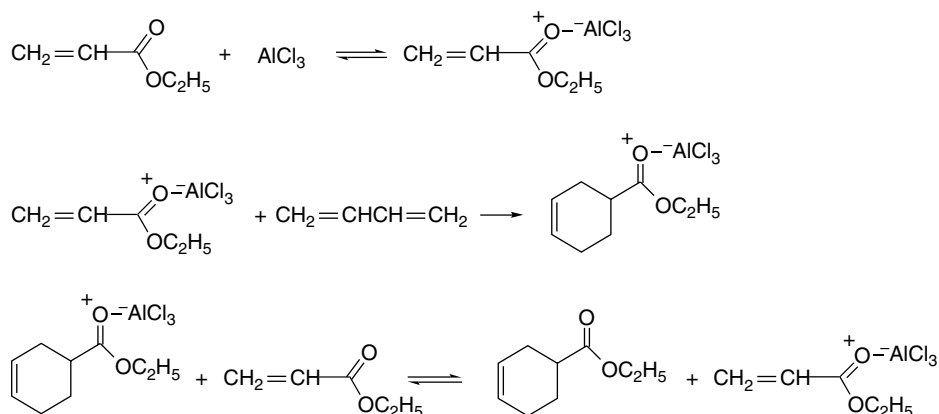


Fig. 3.31. TiCl_4 complex of ethyl lactate.
Reproduced from *Angew. Chem. Int. Ed. Engl.*,
29, 112, by permission of Wiley-VCH.

¹⁴³. S. Shambayati, W. E. Crowe, and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.*, **29**, 256 (1990).

¹⁴⁴. T. Poll, J. O. Melter, and G. Helmchen, *Angew. Chem. Int. Ed. Engl.*, **24**, 112 (1985).

Diels-Alder addition reactions are accelerated by catalytic amounts of a Lewis acid. The complexed ester (ethyl acrylate in the example given) is substantially more reactive than the uncomplexed molecule, and the reaction proceeds through the complex. The reactive complex is regenerated by exchange of the Lewis acid from the adduct. The reaction is accelerated because the dienophile becomes more electrophilic. In MO terminology, the LUMO energy is lowered, resulting in stronger interaction with the diene HOMO.



The strength of the complexation depends on both of the donor atom and the metal ion. The solvent is also an important factor because solvent molecules that are electron donors can compete for the Lewis acid. Qualitative predictions about the strength of donor-acceptor complexation can be made on the basis of the hard-soft-acid-base (HSAB) concept (see Section 1.1.6). The better matched the donor and acceptor, the stronger the complexation. Scheme 3.6 gives an approximate ordering of hardness and softness for some neutral and ionic Lewis acids and bases.

There are more structural variables to consider in catalysis by Lewis acids than in the case of catalysis by protons. In addition to the hard-soft relationship, steric, geometric, and stereoelectronic factors can come into play. This makes the development of an absolute scale of “Lewis acid strength” difficult, since the complexation strength depends on the specific characteristics of the base. There are also variations in the strength of the donor-acceptor bonds. Bond strengths calculated for complexes such as $\text{H}_3\text{N}^+-\text{BF}_3^-$ (22.0 kcal/mol) and $(\text{CH}_3)_3\text{N}^+-\text{BH}_3^-$ (41.1 kcal/mol) are substantially

Scheme 3.6. Relative Hardness and Softness

	Lewis acids		Lewis bases	
	Cationic	Neutral	Neutral	Anionic
Hard	H^+	$\text{BF}_3, \text{AlCl}_3$	H_2O	$\text{F}^-, \text{SO}_4^{2-}$
	$\text{Li}^+, \text{Mg}^{2+}, \text{Ca}^{2+}$	R_3B	Alcohols	Cl^-
	Na^+		Ketones, ethers	Br^-
	$\text{Zn}^{2+}, \text{Cu}^{2+}$		Amines	N_3^-
	$\text{Pd}^{2+}, \text{Hg}^{2+}, \text{Ag}^+$		Sulfides	CN^-
	$\text{RS}^+, \text{RSe}^+$			I^-
Soft	I^+			S^{2-}

Table 3.29. Relative Lewis Acidity^a

Acid	$\Delta H(\text{kcal/mol})^b$	$\pi^*(\text{eV})^c$	NMR $\Delta\delta^d$	Relative acidity
BCl ₃	-6.6	-2.52	1.35	1.00
AlCl ₃	-25.6	-2.31	1.23	0.91
C ₂ H ₅ AlCl ₂	-20.0	-2.03	1.15	0.80
BF ₃	+4.1	-1.93	1.17	0.76
(C ₂ H ₅) ₂ AlCl	-5.6	-1.82	0.91	0.71
(C ₂ H ₅) ₃ Al	-10.1	-1.68	0.63	0.63
SnCl ₄	+10.0	-1.58	0.87	0.61

a. P. Laszlo and M. Teston, *J. Am. Chem. Soc.*, **112**, 8750 (1990).

b. As found by MNDO calculation

c. LUMO π energy in eV.

d. Change of chemical shift of H(3) in butenal.

less than for covalent bonds between similar elements (see also Section 3.4.4). Some Lewis acid-base complexes have weak bonds that are primarily electrostatic in nature (e.g., CH₃CN⁺-BF₃⁻, 9.1 kcal/mol).¹⁴⁵

There have been several efforts to develop measures of Lewis acid strength. One indication of Lewis acid strength of a number of compounds commonly used in synthesis is shown in Table 3.29. The relative acidity values given are derived from the LUMO level of the π^* orbital of the compound, with the BCl₃ complex defined as 1.00 and the uncomplexed but-2-enal LUMO energy taken as 0.¹⁴⁶ These values correlate with ¹H-NMR chemical shift of the H(3) proton of butenal.¹⁴⁷ In contrast, the calculated (MNDO) bond strengths (ΔH) do not correlate with the acid strength.

In another study, the ¹³C chemical shift for acetone in complexes with various Lewis acids was determined (Table 3.30).¹⁴⁸ One general trend that can be noted is the increasing shift with the formal oxidation state of the metal.

A quite broad range of Lewis acid strengths was evaluated by comparing their effect on the shift of the fluorescence of complexes with *N*-methylacridone.¹⁴⁹ The shifts also correlated with the capacity of the Lewis acid to facilitate the reduction of

Table 3.30. ¹³C Chemical Shifts in Lewis Acid Complexes of Acetone

Lewis Acid	¹³ Chemical Shift
—	210
MgCl ₂	221
ZnCl ₂	227
Sc(O ₃ SCF ₃) ₃	239
AlCl ₃	245
SbF ₅	250

¹⁴⁵. V. Jonas, G. Frenking, and M. T. Reetz, *J. Am. Chem. Soc.*, **116**, 8741 (1994).

¹⁴⁶. P. Laszlo and M. Teston, *J. Am. Chem. Soc.*, **112**, 8750 (1990).

¹⁴⁷. R. F. Childs, D. L. Mulholland, and A. Nixon, *Can. J. Chem.*, **60**, 801 (1982).

¹⁴⁸. D. H. Barich, J. B. Nicholas, T. Xu, and J. F. Haw, *J. Am. Chem. Soc.*, **120**, 12342 (1998).

¹⁴⁹. S. Fukuzumi and K. Ohkubo, *J. Am. Chem. Soc.*, **124**, 10270 (2002).

**Table 3.31. Wavelength and Energy Shift in
N-Methylacridone-Lewis Acid Complexes**

Lewis acid	λ_{\max} (nm)	$h\nu_{\text{fl}}$ (eV)
$\text{Fe}(\text{ClO}_4)_3$	478	2.59
$\text{Sc}(\text{O}_3\text{SCF}_3)_3$	474	2.62
$\text{Fe}(\text{ClO}_4)_2$	471	2.63
$\text{Cu}(\text{ClO}_4)_2$	471	2.63
$\text{Yb}(\text{O}_3\text{SCF}_3)_3$	460	2.70
$\text{La}(\text{O}_3\text{SCF}_3)_3$	458	2.71
$\text{Zn}(\text{O}_3\text{SCF}_3)_3$	456	2.72
Ph_3SnCl	455	2.72
Bu_2SnCl_2	453	2.72
$\text{Mg}(\text{ClO}_4)_2$	451	2.75
LiClO_4	442	2.81
NaClO_4	437	2.84
Uncomplexed	432	2.87

O_2 to O_2^- , which is again a measure of the ability to stabilize anionic charge. The fluorescence shifts are given in Table 3.31 and the correlation is shown in Figure 3.32. The orders $\text{Li}^+ > \text{Na}^+$ and $\text{Mg}^{2+} > \text{Ca}^{2+} > \text{Sr}^{2+} > \text{Ba}^{2+}$ show that Lewis acidity decreases with the size of the cation. According to this scale, the tin halides are comparable in acidity to Mg^{2+} . The strong Lewis acidity of Sc^{3+} , Y^{3+} , and the lanthanides, such as La^{3+} and Yb^{3+} , has been exploited in various synthetic applications.

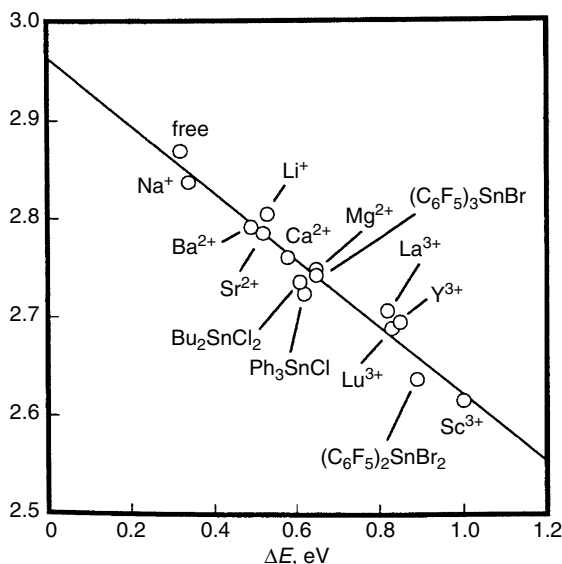


Fig. 3.32. Correlation between fluorescence shift and shift in oxidation energy for several Lewis acids. Reproduced from *J. Am. Chem. Soc.*, **124**, 10270 (2002), by permission of the American Chemical Society.

3.8.1. Bulk Solvent Effects

Since most organic reactions are done in solution, it is important to recognize some of the ways that solvents affect the course and rates of reactions. Some of the more common solvents can be roughly classified as in Table 3.32 on the basis of their structure and dielectric constants. There are important differences between *protic solvents*, those which contain hydrogens that form hydrogen bonds and can exchange rapidly (such as those bonded to oxygen, nitrogen, or sulfur), and *aprotic solvents*, in which all hydrogen is bound to carbon. Similarly, *polar solvents*, those that have high dielectric constants, have effects on reaction rates that are different from nonpolar solvent media.

When discussing solvent effects, it is important to distinguish between the macroscopic effects and those that depend upon details of structure. Macroscopic properties refer to properties of the bulk solvent. One example is the dielectric constant, which is a measure of the ability of the solvent to increase the capacitance of a condenser. Dielectric constants increase with molecular dipole moment and polarizability because of the ability of both the permanent and induced molecular dipole to align with the external electric field. An important property of solvent molecules is the response to changes in charge distribution as reaction occurs. The dielectric constant of a solvent is a good indicator of its ability to accommodate separation of charge. It is not the only factor, however, since, being a macroscopic property, it conveys little information about the ability of the solvent molecules to interact with the solute molecules and ions at close range. These direct solute-solvent interactions depend on the specific structures of the molecules.

Solvents that fall into the nonpolar aprotic class are not very effective at stabilizing the development of charge separation. These molecules have small dipole moments and do not have hydrogens capable of forming hydrogen bonds. Reactions that involve charge separation in the TS therefore proceed more slowly in this class of solvents than in protic or polar aprotic solvents. The reverse is true for reactions in which species having opposite charges come together in the TS. In this case the TS is less highly charged than the individual reactants and reaction is favored by weaker solvation that

Table 3.32. Dielectric Constants (ϵ) and Molecular Dipole Moment (μ) of Some Common Solvents

Aprotic solvents				Protic solvents				
Nonpolar	ϵ	μ	Polar	ϵ	μ		ϵ	μ
Hexane	1.9	0	Pyridine	12	2.21	Acetic acid	6.1	1.7
CCl ₄	2.2	0	Acetone	21	2.88	CF ₃ CO ₂ H	8.6	
Dioxane	2.2	0	HMPA	30		<i>t</i> -Butanol	12.5	1.7
Benzene	2.3	0	Nitromethane	36	3.46	Ammonia	(22)	1.47
Diethyl ether	4.3	1.15	DMF	37	3.82	Ethanol	24.5	1.69
Chloroform	4.8	1.04	Acetonitrile	38	3.92	Methanol	32.7	1.7
THF	7.6	1.75	DMSO	47	3.96	Water	78	1.85

a. Dielectric constants (ϵ) and dipole moments (μ) in debye units from the compilation of solvent properties in J. A. Riddick and W. B. Bunger, eds., *Organic Solvents*, Vol. II of *Techniques of Organic Chemistry*, 3rd Edition, Wiley-Interscience, New York, 1970.

Scheme 3.7. Effect of Solvent Polarity on Reactions of Various Charge Types

1. Neutralization of charge.	
$\delta^- \quad \delta^+$ $A^- + B^- \rightarrow A---B \rightarrow A-B$	Favored by nonpolar solvent
2. Separation of charge.	
$\delta^- \quad \delta^+$ $A-B \rightarrow A---B \rightarrow A^- + B^-$	Favored by polar solvent
3. Neutral reactants and products.	
$A + B \rightarrow A---B \rightarrow A-B$	Relatively insensitive to solvent polarity
4. Relative concentration of charge.	
$\delta^+ \quad \delta^+$ $[A-B]^+ \rightarrow A---B \rightarrow A + B^+$	Slightly favored by polar solvent
5. Relative dispersal of charge.	
$\delta^+ \quad \delta^+$ $A^+ + B \rightarrow A---B \rightarrow [A-B]^+$	Slightly favored by nonpolar solvent

leaves the oppositely charge reactants in a more reactive state. Arguing along these lines, the broad relationships between reactivity and solvent type shown in Scheme 3.7 can be deduced.

Many empirical measures of solvent polarity have been developed.¹⁵⁰ One of the most useful is based on shifts in the absorption spectrum of a reference dye. The position of absorption bands is sensitive to solvent polarity because the electronic distribution, and therefore the polarity, of the excited state is different from that of the ground state. The shift in the absorption maxima reflects the effect of solvent on the energy gap between the ground state and excited state molecules. An empirical solvent polarity measure called $E_T(30)$ is based on this concept.¹⁵¹ Some values for common solvents are given in Table 3.33 along with the dielectric constants for the solvents. It can be seen that a quite different order of polarity is given by these two quantities.

Table 3.33. $E_T(30)$, an Empirical Measure of Solvent Polarity, Compared with Dielectric Constant^a

	$E_T(30)$	ϵ		$E_T(30)$	ϵ
Water	63.1	78	DMF	43.8	37
Trifluoroethanol	59.5		Acetone	42.2	21
Methanol	55.5	32.7	Dichloromethane	41.1	8.9
80:20 Ethanol-water	53.7		Chloroform	39.1	4.8
Ethanol	51.9	24.5	Ethyl acetate	38.1	6.0
Acetic acid	51.2	6.1	THF	37.4	7.6
2-Propanol	48.6	19.9	Diethyl ether	34.6	4.3
Acetonitrile	46.7	38	Benzene	34.5	2.3
DMSO	45.0	47			

From C. Reichardt, *Angew. Chem. Int. Ed. Engl.*, **18**, 98 (1979)

¹⁵⁰ C. Reichardt, *Angew. Chem. Int. Ed. Engl.*, **18**, 98 (1979); C. Reichardt, *Solvent Effects in Organic Chemistry*, Verlag Chemie, Weinheim, 1990; J. Catalan, V. Lopez, P. Perez, R. Martin-Villamil, and J. G. Rodriguez, *Liebigs Ann.*, 241 (1995); C. Laurance, P. Nicolet, M. T. Dalati, J. L. M. Abboud, and R. Notario, *J. Phys. Chem.*, **98**, 5807 (1994).

¹⁵¹ C. Reichardt and K. Dimroth, *Fortshr. Chem. Forsch.*, **11**, 1 (1968); C. Reichardt, *Justus Liebigs Ann. Chem.*, **752**, 64 (1971).

As a specific example of a solvent effect, let us consider how the solvent affects the solvolysis of *t*-butyl chloride. Much evidence, which is discussed in detail in Chapter 4, indicates that the rate-determining step of the reaction is ionization of the carbon-chlorine bond to give a carbocation and the chloride ion. The TS reflects some of the charge separation that occurs in the ionization:

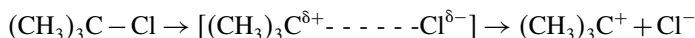


Figure 3.33 is a schematic interpretation of the solvation changes that take place during the ionization of *t*-butyl chloride, with S representing surrounding solvent molecules. With the neutral slightly polar reactant, there is only weak solvation. As charge separation develops in the TS, solvent molecules align with the most favorable orientation of the dipoles. The charged ions are strongly solvated.

The bulk dielectric constant may be a poor indicator of the ability of solvent molecules to facilitate the charge separation in the TS. The fact that the carbon and chlorine remain partially bonded at the TS prevents the solvent molecules from actually intervening between the developing centers of charge. Instead, the solvent molecules must stabilize the charge development by acting around the periphery of the activated complex. The nature of this interaction depends upon the detailed structure of the activated complex and solvent. The ability of solvents to stabilize the TS of *t*-butyl chloride ionization has been measured by comparing the rate of the reaction in the different solvent mixtures. The solvents were then assigned *Y* values, with the reference solvent taken as 80:20 ethanol-water. The *Y* value of other solvents is defined by the equation

$$\log \frac{k_{\text{solvent}}}{k_{80\% \text{ ethanol}}} = Y \quad (3.59)$$

Table 3.34 lists the *Y* values for some alcohol-water mixtures and for some other solvents. The *Y* value reflects primarily the ionization power of the solvent. It is largest for polar solvents such as water and formic acid and becomes progressively smaller and eventually negative as the solvent becomes less polar and contains more (or larger) nonpolar alkyl groups. Note that among the solvents listed there is a spread of more than 10^6 in the measured rate of reaction between *t*-butyl alcohol ($Y = -3.2$) and water ($Y = +3.49$). This large range of reaction rates demonstrates how important solvent effects can be.

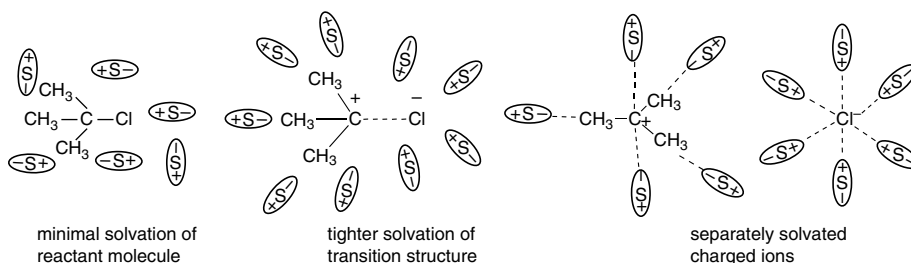


Fig. 3.33. Schematic representation of solvation changes during ionization of *t*-butyl chloride.

Table 3.34. Y Values for Some Solvent Systems.^a

Ethanol-water	Y	Methanol-water	Y	Other solvents	Y
100:0	-2.03	100:0	-1.09	Acetic acid	-1.64
80:20	0.00	80:20	0.38	Formic acid	2.05
50:50	1.65	50:50	1.97	<i>t</i> -Butyl alcohol	-3.2
20:80	3.05	10:90	3.28	90:10 acetone:water	-1.85
0:100	3.49			90:10 dioxane:water	-2.03

a. From A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, **78**, 2770 (1956).

Several other treatments of solvent effects on solvolysis rates have been developed.¹⁵² The equations typically include several terms related to: (a) macroscopic nonspecific solvent properties, such as the dipole moment and dielectric constant; (b) empirical polarity criteria, such as $E_T(30)$; (c) solvent electrophilicity and nucleophilicity parameters; and (d) terms related to solvent *cohesivity*. The last term accounts for the difference in work required to disrupt structure within the solvent, when, for example, there is expansion in volume between reactants and the TS.

3.8.2. Examples of Specific Solvent Effects

The electrostatic solvent effects discussed in the preceding paragraphs are not the only possible modes of interaction of solvent with reactants and TS. Specific structural effects may cause either the reactants or the TS to be particularly strongly solvated. Figure 3.34 shows how such solvation can affect the relative energies of the ground state and the TS and cause rate variations from solvent to solvent. Unfortunately, no

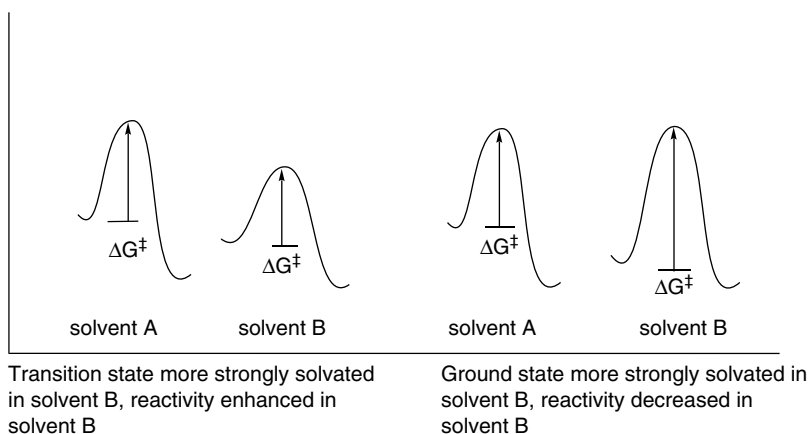


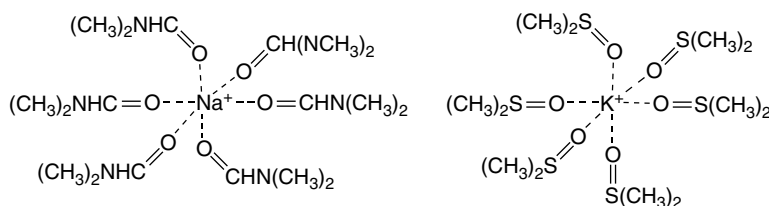
Fig. 3.34. Reaction energy profiles showing effect on E_a of (a) preferred solvation of the transition state and (b) preferred solvation of reactants.

¹⁵² G. F. Dvorko, A. J. Vasil'kevich, E. A. Ponomareva, and J. V. Koschii, *Russ. J. Gen. Chem.*, **70**, 724 (2000); I. A. Koppel and V. Palm, *Advances in. Linear Free Energy Relationships*, N. B. Chapman and J. Shorter, eds., Plenum Press, New York, 1972, Chap. 5.; M. H. Abraham, R. W. Taft, and M. J. Kamlet, *J. Org. Chem.*, **46**, 3053 (1981); M. H. Abraham, R. M. Doherty, M. J. Kamlet, J. M. Harris, and R. W. Taft, *J. Chem. Soc., Perkin Trans.*, **2**, 913 (1987); M. R. C. Goncalves, A. M. N. Simoes, and L. M. P. C. Albuquerque, *J. Chem. Soc., Perkin Trans.*, **2**, 1379 (1990).

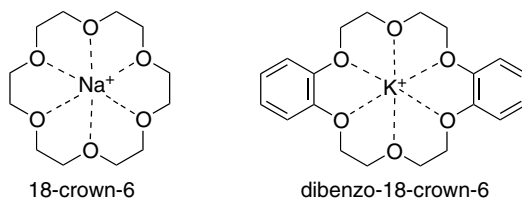
general theory for quantitatively predicting such specific effects has been developed to date. Nevertheless, there are many cases where specific interactions with solvent molecules strongly influence the outcome and/or the rate of reactions.

3.8.2.1. Enhanced Nucleophilicity in Polar Aprotic Solvents. An important example of solvent effects is the enhanced nucleophilicity of many anions in polar aprotic solvents as compared with protic solvents.¹⁵³ In protic solvents, anions are strongly solvated by hydrogen bonding. This is particularly true for hard anions that have a high concentration of charge on oxygen such as alkoxide ions. Hydrogen-bonding decreases the ability of the nucleophile to act as an electron donor. Stated another way, the energy required to disrupt hydrogen bonding adds to the activation energy of the reaction.

In polar aprotic solvents, no hydrogens suitable for hydrogen bonding are present. As a result, the electrons of the anion are more available for reaction. The anion is at a higher energy level because of the small stabilization by the solvent. The polarity of the aprotic solvents is also important for the solubility of ionic compounds. Dissolved ionic compounds are likely to be present as ion pairs or larger aggregates in which the reactivity of the anion is diminished by the electrostatic interaction with the cation. Energy must be expended against this electrostatic attraction to permit the anion to react as a nucleophile. Metal cations such as K^+ and Na^+ are strongly solvated by polar aprotic solvents such as DMSO and DMF. The oxygen atoms in these molecules act as electron donors toward the cations. The dissolved salts are dissociated, and as a result the anions are more reactive because they are poorly solvated and not associated with cations.

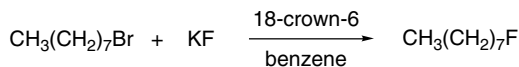


3.8.2.2. Crown Ether and Phase Transfer Catalysts Particularly striking examples of the effect of specific solvation occur with the *crown ethers*. These macrocyclic polyethers specifically solvate cations such as Na^+ and K^+ .



¹⁵³ A. J. Parker, *Q. Rev. Chem. Soc.*, **16**, 163 (1962); C. D. Ritchie, in *Solute-Solvent Interactions*, J. F. Coetzee and C. D. Ritchie, eds., Marcel Dekker, New York, 1969, Chap. 4; E. Buncl and H. Wilson, *Adv. Phys. Org. Chem.*, **14**, 133 (1977).

When added to nonpolar solvents, the crown ethers increase the solubility of ionic materials. For example, in the presence of 18-crown-6, potassium fluoride is soluble in benzene and acts as a reactive nucleophile:



Ref. 154

In the absence of the polyether, potassium fluoride is insoluble in benzene and unreactive toward alkyl halides. Similar enhancement of solubility and reactivity of other salts is observed in the presence of crown ethers. The solubility and reactivity enhancement results because the ionic compound is dissociated to a tightly complexed cation and a “naked” anion. Figure 3.35 shows the tight coordination that can be achieved with a typical crown ether. The complexed cation, because it is surrounded by the nonpolar crown ether, has high solubility in the nonpolar media. To maintain electroneutrality the anion is also transported into the solvent. The cation is shielded from close interaction with the anion because of the surrounding crown ether molecule. As a result, the anion is unsolvated and at a relatively high energy and therefore highly reactive.

A related solvation phenomenon is the basis for *phase transfer catalysis*.¹⁵⁵ The catalysts here are salts in which one of the ions (usually the cation) has large nonpolar substituent groups that confer good solubility in organic solvents. The most common examples are tetraalkylammonium and tetraalkylphosphonium ions. In two-phase systems consisting of water and a nonpolar organic solvent, these cations are extracted into the organic phase and, as a result of electrostatic forces, anions are transferred to the organic phase. The anions are weakly solvated and display high reactivity. Reactions are carried out between a salt containing the desired nucleophilic anion and

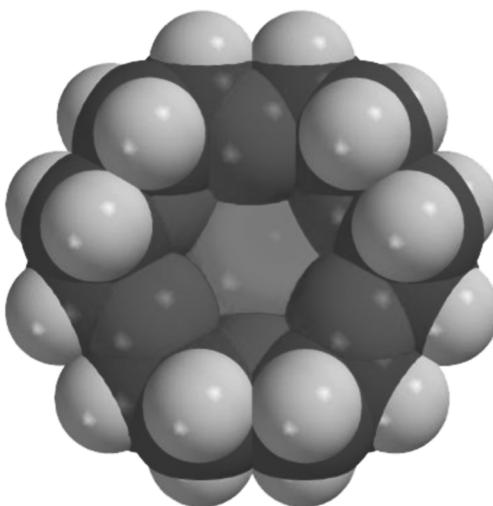
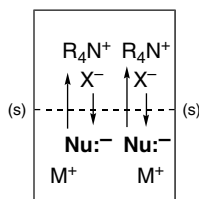


Fig. 3.35. Space-filling molecular model depicting a metal cation complexed by 18-crown-6. (See also color insert.)

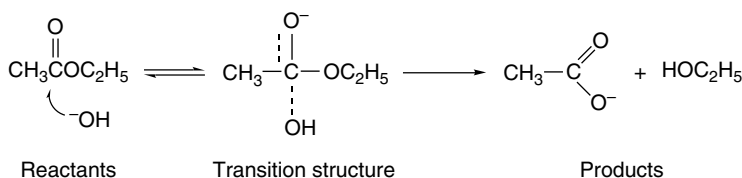
¹⁵⁴. C. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, **96**, 2250 (1974).

¹⁵⁵. C. M. Starks, C. L. Liotta, and M. Halpern, *Phase Transfer Catalysis: Fundamentals: Applications and Industrial Perspectives*, Chapman and Hall, New York, 1994.

an organic reactant, typically in a hydrocarbon or nonpolar halogenated solvent. The addition of phase transfer catalysts causes migration of the anion into the organic phase and, because of its high nucleophilicity, reaction occurs under exceptionally mild conditions.



3.8.2.3. Differential Solvation of Reactants and Transition States. It should always be kept in mind that solvent effects can modify the energy of both the reactants and the transition state. It is the *difference* in the solvation that is the basis for changes in activation energies and reaction rates. Thus, although it is common to discuss solvent effects solely in terms of reactant solvation or transition state solvation, this is an oversimplification. A case that illustrates this point is the base-promoted hydrolysis of esters by hydroxide ion.



The reaction is faster in DMSO-water than in ethanol-water. Reactant solvation can be separated from transition state solvation by calorimetric measurement of the heat of solution of the reactants in each solvent system. The data in Figure 3.36 compare the energies of the reactants and TS for ethyl acetate and hydroxide ion reacting in aqueous ethanol versus aqueous DMSO. It can be seen that both the reactants and the TS are more strongly solvated in the ethanol-water medium.¹⁵⁶ The enhancement

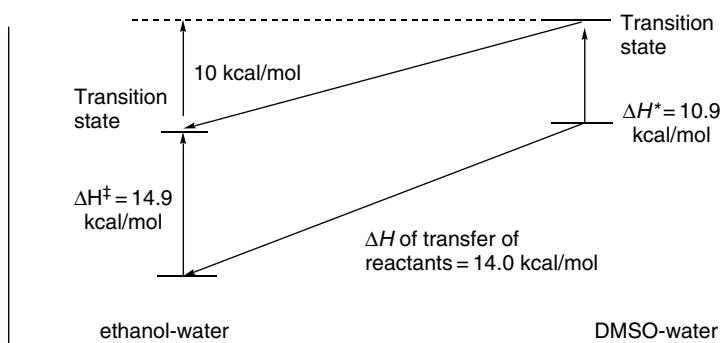
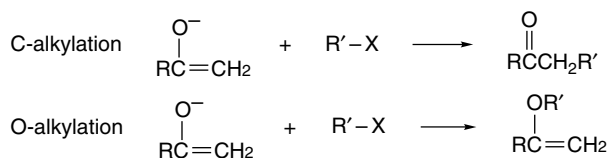


Fig. 3.36. Comparative reactant and transition state solvation in the reaction of ethyl acetate with hydroxide ion in ethanol/water and DMSO. Data from *J. Am. Chem. Soc.*, **94**, 71 (1972).

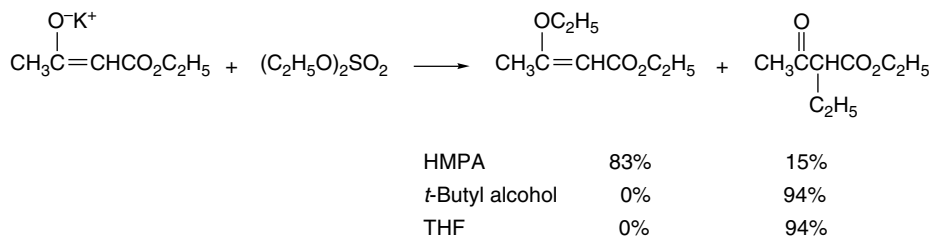
¹⁵⁶ P. Haberfield, J. Friedman, and M. F. Pinkson, *J. Am. Chem. Soc.*, **94**, 71 (1972).

in reaction rate comes from the fact that the difference is greater for the small hard hydroxide ion than for the larger anionic species present at the transition state.¹¹⁶ It is generally true that solvation forces are strongest for the small, hard anions and decrease with size and softness.

3.8.2.4. Oxygen versus Carbon Alkylation in Ambident Enolate Anions. Enolate anions are *ambident nucleophiles*. Alkylation of an enolate can occur at either carbon or oxygen. Since most of the negative charge of an enolate is on the oxygen atom, it might be supposed that O-alkylation would dominate. A number of factors other than charge density affect the C/O-alkylation ratio and it is normally possible to establish reaction conditions that favor alkylation on carbon.



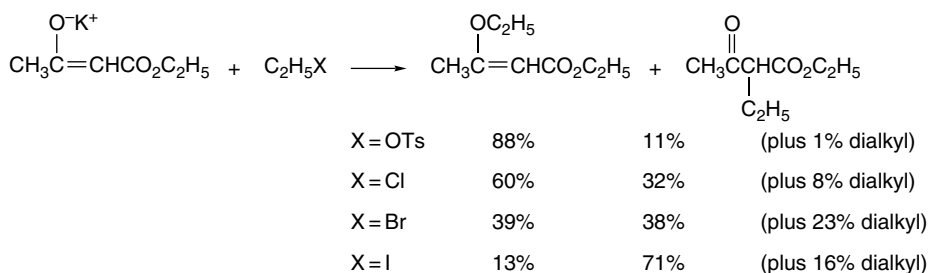
O-Alkylation is most pronounced when the enolate is least solvated. When the potassium salt of ethyl acetoacetate is treated with ethyl sulfate in the polar aprotic solvent HMPA, the major product (83%) results from O-alkylation. In THF, where ion clustering occurs, all of the product is C-alkylated. In *t*-butyl alcohol, where the acetoacetate anion is hydrogen bonded by solvent, again only C-alkylation is observed.¹⁵⁷



Higher C/O ratios are observed with alkyl halides than with alkyl sulfonates and sulfates. The highest C/O-alkylation ratios are given by alkyl iodides. For ethylation of potassium ethyl acetoacetate in HMPA the product compositions shown below were obtained.¹⁵⁸

¹⁵⁷ A. L. Kurts, A. Masias, N. K. Genkina, I. P. Beletskaya, and O. A. Reutov, *Dokl. Akad. Nauk. SSSR* (Engl. Transl.), **187**, 595 (1969).

¹⁵⁸ A. L. Kurts, N. K. Genkina, A. Masias, I. P. Beletskaya, and O. A. Reutov, *Tetrahedron*, **27**, 4777 (1971).



Leaving-group effects on the ratio of C- to O-alkylation can be correlated by the HSAB rationale.¹⁵⁹ Of the two nucleophilic sites in an enolate ion, oxygen is harder than carbon. Nucleophilic substitution reactions of the S_N2 type proceed best when the nucleophile and leaving group are either both hard or both soft.¹⁶⁰ Consequently, ethyl iodide, with the soft leaving group iodide, reacts preferentially with the softer carbon site rather than the harder oxygen. Oxygen-leaving groups, such as sulfonate and sulfate, are harder and react preferentially at the hard oxygen site of the enolate. The hard-hard combination is favored by an early transition state where the electrostatic attraction is the most important factor. The soft-soft combination is favored by a later transition state where partial bond formation is the dominant factor. The C-alkylation product is more stable than the O-alkylation product (because the bond energy of $\text{C}=\text{O} + \text{C}-\text{C}$ is greater than $\text{C}=\text{C} + \text{C}-\text{O}$), as illustrated in Figure 3.37.

Similar effects are also seen with enolates of simple ketones. For isopropyl phenyl ketone, the inclusion of one equivalent of 12-crown-4 in a DME solution of the lithium enolate changes the C:O ratio from 1.2:1 to 1:3, using methyl sulfate as the alkylating agent.¹⁶¹ The crown ether selectively solvates the Li^+ ion, leaving the anion in a more

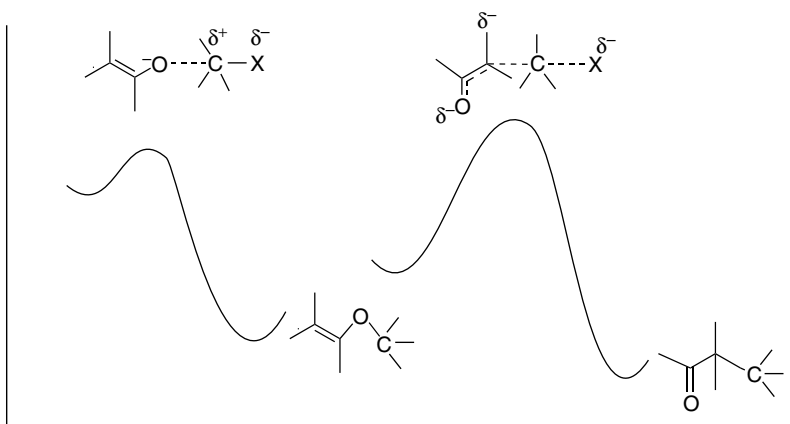


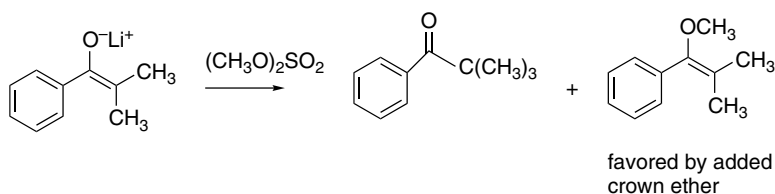
Fig. 3.37. Differential reaction energy profiles for O versus C alkylation of enolates. (a) O-Alkylation is characterized by an early transition state, weak O-solvation, high anion reactivity, and relatively large electrostatic effects. (b) C-Alkylation is characterized by a later transition state with more C–C bond formation and more diffuse charge distribution.

¹⁵⁹. T. -L. Ho, *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York (1977).

¹⁶⁰. R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967).

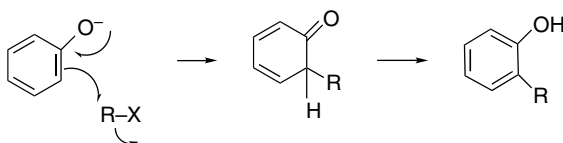
¹⁶¹. L. M. Jackman and B. C. Lange, *J. Am. Chem. Soc.*, **103**, 4494 (1981).

reactive state. With methyl iodide as the alkylating agent, C-alkylation is strongly favored with or without 12-crown-4.

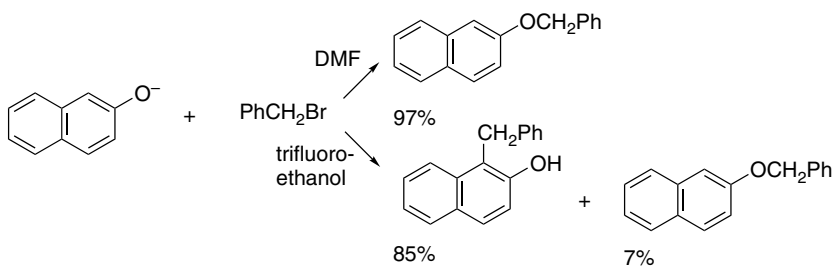


To summarize, the amount of O-alkylation is maximized by use of an alkyl sulfate or alkyl sulfonate in a polar aprotic solvent. The amount of C-alkylation is maximized by using an alkyl halide in a less polar or protic solvent. The majority of synthetic operations involving ketone enolates are carried out in THF or DME using an alkyl bromide or alkyl iodide and C-alkylation is favored.

Phenoxide ions are a special case related to enolate anions and have a strong preference for O-alkylation because C-alkylation disrupts aromatic conjugation.

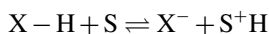


Phenoxides undergo O-alkylation in solvents such as DMSO, DMF, ethers, and alcohols. However, in water and trifluoroethanol there is extensive C-alkylation.¹⁶² These latter solvents form particularly strong hydrogen bonds with the oxygen atom of the phenolate anion. This strong solvation decreases the reactivity at oxygen and favors C-alkylation.



Topic 3.1. Acidity of Hydrocarbons

One of the fundamental properties of compounds containing hydrogen is their ability to act as proton donors, that is, as *Brønsted acids*.



¹⁶² N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Am. Chem. Soc.*, **85**, 1141 (1963); N. Kornblum, R. Seltzer, and P. Haberfield, *J. Am. Chem. Soc.*, **85**, 1148 (1963).

The concept of acidity was discussed earlier in relation to aqueous solutions and the acidity of carboxylic acids and alcohols (see p. 321–322). The acidity of such compounds can be measured and expressed as the pK_a .

$$pK_a = -\log K \text{ where } K = \frac{[S^+H][X^-]}{[HX][S]}$$

Determination of the acidity of hydrocarbons is more difficult. As most are very weak acids, very strong bases are required to cause deprotonation. Water and alcohols are far more acidic than most hydrocarbons and are unsuitable solvents for generation of hydrocarbon anions. A strong base deprotonates the solvent rather than the hydrocarbon. For synthetic purposes, aprotic solvents such as ether, THF, and dimethoxyethane are used, but for equilibrium measurements solvents that promote dissociation of ion pairs and ion clusters are preferred. Weakly acidic solvents such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and cyclohexylamine are used in the preparation of moderately basic carbanions. The high polarity and cation-solvating ability of DMSO and DMF facilitate dissociation of ion pairs so that the equilibrium data obtained refer to the free ions, rather than to ion aggregates.

The basicity of a base-solvent system can be specified by a basicity constant H_- . The H_- is a measure of solution basicity, analogous to the acidity function H_0 (see Section 3.7.1.3). The value of H_- approximates the pH of strongly basic solutions. The larger the value of H_- , the greater the proton-abstracting ability of the medium. Use of a series of overlapping indicators permits assignment of H_- values to base-solvent systems, and allows pK 's to be determined over a range of 0–30 pK units. Table 3.35 presents H_- values for some solvent-base systems.

The acidity of a hydrocarbon can be determined in an analogous way.¹⁶³ If the electronic spectra of the neutral and anionic forms are sufficiently different, the concentrations of each can be determined directly, and the position of the equilibrium constant is related to pK by the equation

$$pK_{R-H} = H_- + \log \frac{[R-H]}{[R^-]}$$

A measurement of the ratio $[RH] : [R^-]$ at a known H_- yields the pK . If the electronic spectrum of the hydrocarbon and its anion are not sufficiently different, an indicator is

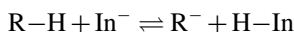
Table 3.35. Values of H_- for Some Solvent-Base Systems

Solvent	H_-^a
5M KOH	15.5
10M KOH	17.0
1M KOH	18.5
0.01M NaOMe in 1:1 DMSO-MeOH	15.0
0.01M NaOMe in 10:1 DMSO-MeOH	18.0
0.01M NaOEt in 20:1 DMSO-MeOH	21.0

a. From J. R. Jones, *The Ionization of Carbon Acids*, Academic Press, New York, 1973, Chap. 6.

¹⁶³ D. Dolman and R. Stewart, *Can. J. Chem.*, **45**, 911 (1967); E. C. Steiner and J. M. Gilbert, *J. Am. Chem. Soc.*, **87**, 382 (1965); K. Bowden and R. Stewart, *Tetrahedron*, **21**, 261 (1965).

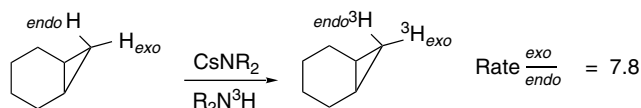
used and its spectrum is monitored. Equilibrium is established between the indicator and hydrocarbon in the basic medium. The relationship



then provides a way to relate the concentrations that are not directly measured—[RH] and [R[−]][−]to quantities that are—[HIn] and [In[−]].

The p*K* values are influenced by the solvent and other conditions of the measurement. The extent of ion pairing is a function of the ability of the solvent to solvate the ionic species. Ion pairing is greatest in nonpolar solvents such as ethers. In dipolar aprotic solvents, especially DMSO, ion pairing is much less likely to be significant.¹⁶⁴ The identity of the cation present can also have a significant effect if ion pairs are present. Owing to these factors, the numerical p*K* values are not absolute and are specific to the solvent. Nevertheless, they provide a useful measure of relative acidity. The two solvents that have been used for most quantitative measurements on weak carbon acids are cyclohexylamine and DMSO. Some of these values are given in Table 3.36. It is not expected that the values will be numerically identical with aqueous p*K*_a, but for most compounds the same relative order of acidity is observed for hydrocarbons of similar structural type.

A number of hydrocarbons have been studied in cyclohexylamine using cesium cyclohexylamide as the base. For many of the compounds studied, spectroscopic measurements were used to determine the relative extent of deprotonation of two hydrocarbons and thus establish relative acidity.¹⁶⁵ For other hydrocarbons, the acidity was derived by kinetic measurements. Such studies are usually done by observing the rate of isotopic exchange (deuterium or tritium) at the site of interest. The rate of hydrocarbon exchange can be measured using ³H NMR spectroscopy.¹⁶⁶ The course of exchange can be followed by the appearance of the ³H NMR signal corresponding to the hydrogen undergoing exchange. For example, the rates of exchange of both the *exo* and *endo* hydrogens in norcaradiene can be followed.



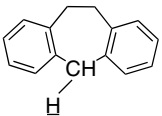
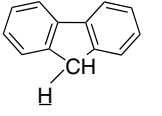
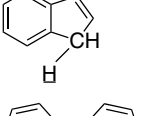
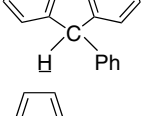
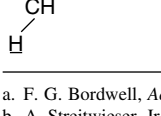
It has been found that there is often a correlation between the rate of proton abstraction (kinetic acidity) and the thermodynamic stability of the carbanion (thermodynamic acidity). Owing to this relationship, kinetic measurements can be used to construct orders of hydrocarbon acidities. These kinetic measurements have the advantage of not requiring the presence of a measurable concentration of the carbanion at any time; instead, the relative ease of carbanion formation is judged from the rate

¹⁶⁴ E. M. Arnett, T. C. Moriarity, L. E. Small, J. P. Rudolph, and R. P. Quirk, *J. Am. Chem. Soc.*, **95**, 1492 (1973); T. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.*, **88**, 307 (1966).

¹⁶⁵ A. Streitwieser, Jr., J. R. Murdoch, G. Hafelinger, and C. J. Chang, *J. Am. Chem. Soc.*, **95**, 4248 (1973); A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *J. Am. Chem. Soc.*, **89**, 63 (1967); A. Streitwieser, Jr., E. Juaristi, and L. L. Nebenzahl, in *Comprehensive Carbanion Chemistry*, Part A, E. Bunzel and T. Durst, eds., Elsevier, New York, 1980, Chap. 7.

¹⁶⁶ R. E. Dixon, P. G. Williams, M. Saljoughian, M. A. Long, and A. Streitwieser, *Magn. Res. Chem.*, **29**, 509 (1991).

Table 3.36. Acidity of Some Hydrocarbons

Hydrocarbon	K ⁺ (DMSO) ^a	Cs ⁺ (cyclohexylamine) ^b	Cs ⁺ (THF) ^c
PhCH ₂ -H	43	41.2	40.9
Ph ₂ CH-H	32.4	33.4	33.3
Ph ₃ C-H	30.6	31.4	31.3
		31.2	
	22.6	22.7	22.9
	20.1	19.9	22.9
	17.9	18.5	18.2
	18.1	16.6 ^{d,e}	

a. F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456, 463 (1988).

b. A. Streitwieser, Jr., J. R. Murdoch, G. Hafelinger, and C. J. Chang, *J. Am. Chem. Soc.*, **95**, 4248 (1973); A. Streitwieser, Jr., and F. Guibe, *J. Am. Chem. Soc.*, **100**, 4532 (1978).

c. M. J. Kaufman, S. Gronert, and A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **110**, 2829 (1988); A. Streitwieser, J. C. Ciula, J. A. Krom, and G. Thiele, *J. Org. Chem.*, **56**, 1074 (1991).

d. A. Streitwieser, Jr., and L. L. Nebenzahl, *J. Am. Chem. Soc.*, **98**, 2188 (1976).

e. The pK of cyclopentadiene in water is 16.0

at which exchange occurs. This method is applicable to very weak acids, for which no suitable base will generate a measurable carbanion concentration. This method was used to extend the scale to hydrocarbons such as toluene, for which the exchange rate, but not equilibrium data, can be obtained.¹⁶⁷

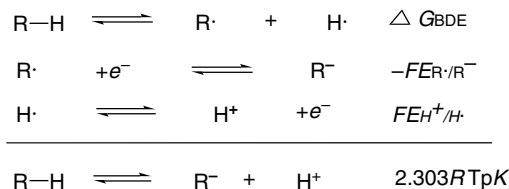
For synthetic purposes, carbanions are usually generated in ether solvents, often THF or dimethoxyethane. There are relatively few quantitative data available on hydrocarbon acidity in such solvents. Table 3.36 contains several entries for Cs⁺ salts in THF. The numerical values are scaled with reference to the pK of fluorene of 22.9.¹⁶⁸

¹⁶⁷. A. Streitwieser, Jr., M. R. Granger, F. Mares, and R. A. Wolf, *J. Am. Chem. Soc.*, **95**, 4257 (1973).

¹⁶⁸. M. J. Kaufman, S. Gronert, and A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **110**, 2829 (1988); A. Streitwieser, Jr., J. C. Ciula, J. A. Krom, and G. Thiele, *J. Org. Chem.*, **56**, 1074 (1991).

Allylic conjugation stabilizes carbanions and pK values of 43 (in cyclohexylamine)¹⁶⁹ and 47–48 (in THF-HMPA)¹⁷⁰ have been determined for propene. On the basis of exchange rates with cesium cyclohexylamide, cyclohexene and cycloheptene have been found to have pK values of about 45 in cyclohexylamine.¹⁷¹ The hydrogens on the sp^2 carbons in benzene and ethylene are more acidic than the hydrogens in saturated hydrocarbons. A pK of 43 has been estimated for benzene on the basis of extrapolation from a series of fluorobenzenes.¹⁷² Electrochemical measurements have been used to establish a lower limit of about 46 for the pK of ethylene.¹⁷⁰

For saturated hydrocarbons, exchange is too slow and reference points are so uncertain that direct determination of pK values by exchange measurements is not feasible. The most useful approach to obtain pK data for such hydrocarbons involves making a measurement of the electrochemical potential for the one electron reduction of the hydrocarbon radical. From this value and known C–H bond dissociation energies, pK values can be calculated.



Early application of these methods gave estimates of the pK of toluene of about 45 and propene of about 48. Methane was estimated to have a pK in the range of 52–62.¹⁷⁰ More recent electrochemical measurements in DMF provided the results in Table 3.37.¹⁷³ These measurements put the pK of methane at about 48, with benzylic and allylic stabilization leading to values of 39 and 38 for propene and toluene, respectively. The electrochemical values that overlap with the pK_{DMSO} scale for compounds such as diphenylmethane and triphenylmethane are in reasonable agreement.

Most of the hydrocarbons included in Tables 3.36 and 3.37 illustrate the effect of *anion stabilization*. Cyclopentadiene is the most striking example. The pK is similar to that of alcohols. The high relative acidity of cyclopentadiene is due to the *aromatic*

Table 3.37. pK Values for Weakly Acidic Hydrocarbons Based on Reduction Potentials in DMF^a

	pK		pK
CH_3-H	48	$CH_2=CHCH_2-H$	38
CH_3CH_2-H	51	$CH_2=CHC(CH_3)-H$	38
$(CH_3)_2CH-H$	50	$HC\equiv CCH_2-H$	38
$(CH_3)_3C-H$	49	$PhCH_2-H$	39
cyclopentane	49	Ph_2CH-H	31
cyclohexane	49	Ph_3C-H	29

a. K. Daasbjerg, *Acta Chem. Scand.*, **49**, 578 (1995).

¹⁶⁹. D. W. Boerth and A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **103**, 6443 (1981).

¹⁷⁰. B. Jaun, J. Schwarz, and R. Breslow, *J. Am. Chem. Soc.*, **102**, 5741 (1980).

¹⁷¹. A. Streitwieser, Jr., and D. W. Boerth, *J. Am. Chem. Soc.*, **100**, 755 (1978).

¹⁷². A. Streitwieser, Jr., P. J. Scannon, and H. M. Niemeyer, *J. Am. Chem. Soc.*, **94**, 7936 (1972).

¹⁷³. K. Daasbjerg, *Acta Chem. Scand.*, **49**, 878 (1995).

stabilization of the anion. Indene and fluorene derivatives also benefit from stabilization of the cyclopentadienide rings that are incorporated into their structures. The much greater acidity of fluorene relative to dibenzocycloheptatriene (Table 3.36) reflects the aromatic stabilization of the cyclopentadienide ring in the anion of fluorene. Toluene, diphenylmethane, and triphenylmethane anions are also stabilized by delocalization of the negative charge. Note, however, that the third phenyl substituent has only a small effect on the acidity of triphenylmethane, which presumably reflects steric problems that preclude optimal alignment of the rings in the carbanion.

Another factor that influences hydrocarbon acidity is hybridization at the carbon atom. Acidity increases sharply in the order $sp^3\text{C-H} < sp^2\text{C-H} < sp\text{C-H}$. Terminal alkynes are among the most acidic of the hydrocarbons. For example, in DMSO, phenylacetylene is found to have a pK near 26.5.¹⁷⁴ In cyclohexylamine, the value is 23.2.¹⁷⁵ An estimate of the pK in aqueous solution of 20 is based on a Brønsted relationship.¹⁷⁶ The relatively high acidity of alkynes is associated with the high s character of the C–H bond. The s character is 50%, as opposed to 25% in sp^3 bonds. The electrons in orbitals with high s character experience decreased shielding of the nuclear charge. The carbon is therefore effectively more electronegative, as viewed from the proton sharing an sp hybrid orbital, and hydrogens on sp carbons exhibit greater acidity. This same effect accounts for the relatively high acidity of the hydrocarbons on cyclopropane and other strained rings that have increased s character in the C–H bonds.¹⁷⁷ There is a correlation between the coupling constant $J^1\text{H}-^{13}\text{C}$ and acidity, because the $J^1\text{H}-^{13}\text{C}$ coupling constant is related to hybridization.¹⁷⁸ The relationship between hybridization and acidity may not be as straightforward as suggested by the correlations for alkynes, alkenes, cyclopropane, and alkanes. Sauers tabulated % s character for 28 hydrocarbons and found relatively poor correlation with % s character.¹⁷⁹

Cubane has had an interesting place in the discussion of the correlation between C–H acidity and carbon hybridization. Its acidity was measured by the ^3H exchange NMR technique and found to be about 6.6×10^4 as reactive as benzene.¹⁸⁰ An experimental gas phase measurement of the proton affinity (PA) as 404 kcal/mol is available.¹⁸¹ (See Tables 3.14 and 3.38 for comparable data on other hydrocarbons.) Both of these values indicate that cubane is somewhat more acidic than expected on the basis of the carbon hybridization. There appears to be unusual hybridization of the anion in this case. An AIM analysis suggests that the C–C bond paths in the anion are *less than* 90° , suggesting that the bonds bend inward toward the center of the ring. Sauers also noted an *increase* in s character on going from the hydrocarbon to the anion.¹⁷⁹ Of the 28 deprotonations he examined, only cyclopropane and bicyclo[1.1.1]pentane also showed increased s character in the anion.

¹⁷⁴. F. G. Bordwell and W. S. Matthews, *J. Am. Chem. Soc.*, **96**, 1214 (1974).

¹⁷⁵. A. Streitwieser, Jr., and D. M. E. Reuben, *J. Am. Chem. Soc.*, **93**, 1794 (1971).

¹⁷⁶. D. B. Dahlberg, M. A. Kuzemko, Y. Chiang, A. J. Kresge, and M. F. Powell, *J. Am. Chem. Soc.*, **105**, 5387 (1983).

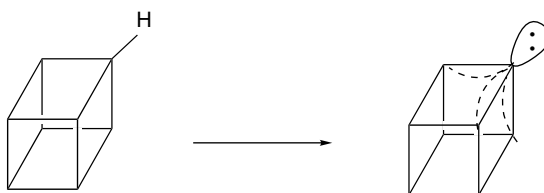
¹⁷⁷. A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *J. Am. Chem. Soc.*, **91**, 529 (1969); G. L. Closs and R. B. Larrabee, *Tetrahedron Lett.*, 287 (1965); M. Randic and Z. Mossic, *Chem. Rev.*, **72**, 43 (1972).

¹⁷⁸. M. A. Battiste and J. M. Coxon, *The Chemistry of the Cyclopropyl Group*, Z. Rapoport, ed., John Wiley & Sons, New York, 1987, pp. 255–305.

¹⁷⁹. R. R. Sauers, *Tetrahedron*, **55**, 10013 (1999).

¹⁸⁰. A. Streitwieser, L. Xie, P. Speers, and P. G. Williams, *Magn. Res. Chem.*, **36**, S509 (1996).

¹⁸¹. M. Hare, T. Emrick, P. E. Eaton, and S. R. Kass, *J. Am. Chem. Soc.*, **119**, 237 (1997).



As we discussed in Section 3.4.2, measurements in the gas phase, which eliminate the effect of solvation, show structural trends that parallel measurements in solution but with larger absolute energy differences. Table 3.38 gives ΔH of gas phase proton dissociation data for some key hydrocarbons. These data show a correspondence with the hybridization and delocalization effects observed in solution. The very large heterolytic dissociation energies reflect both the inherent instability of the carbanions and also the electrostatic attraction between the oppositely charged carbanion and proton that separate.

There have been several studies aimed at using computations to examine hydrocarbon acidity. The proton affinity values for a number of hydrocarbons were calculated by both *ab initio* and DFT methods.¹⁷⁹ Some of the results are shown in Table 3.39.

Alkorta and Elguero found that there is good correlation between PAs calculated by B3LYP/6-311 + +G** computations and available gas phase experimental measurements.¹⁸² There was also good correlation with solution *pK* values. Based on these correlations, they made the interesting prediction that the as yet unknown hydrocarbon tetrahedrane would be comparable to water in acidity.

Knowledge of the structure of carbanions is important to understanding the stereochemistry, stability, and reactivity. Theoretical calculations at the *ab initio* level (HF/4-31G) indicate a pyramidal geometry at carbon in the methyl and ethyl anions. The optimum H—C—H angle in these two carbanions was calculated to be 97°–100°. An interesting effect is observed in that the PA (basicity) of methyl anion decreases in a regular manner as the H—C—H angle is decreased.¹⁸³ This increase in acidity with decreasing internuclear angle has a parallel in small-ring compounds, in which the acidity of hydrogens is substantially greater than in compounds having tetrahedral geometry at carbon. Pyramidal geometry at carbanions can also be predicted on the

**Table 3.38. Enthalpy of Proton
Dissociation for Some Hydrocarbons
(Gas Phase)**

Hydrocarbon	Enthalpy (kcal/mol)
Methane	418.8
Ethene	407.5
Cyclopropane	411.5
Benzene	400.8
Toluene	381.0

a. S. T. Gaul and R. R. Squires, *J. Am. Chem. Soc.*, **112**, 2517 (1990).

¹⁸². I. Alkorta and J. Elguero, *Tetrahedron*, **53**, 9741 (1997).

¹⁸³. A. Streitwieser, Jr., and P. H. Owens, *Tetrahedron Lett.*, 5221 (1973); A. Streitwieser, Jr., P. H. Owens, R. A. Wolf, and J. E. Williams, Jr., *J. Am. Chem. Soc.*, **96**, 5448 (1974); E. D. Jemmis, V. Buss, P. v. R. Schleyer, and L. C. Allen, *J. Am. Chem. Soc.*, **98**, 6483 (1976).

Table 3.39. Computed Proton Affinity for Some Hydrocarbons in kcal/mol^a

Hydrocarbon	MP2/6-31+G(d,p)	B3LYP/6-311++G(2d,p)	Experimental
CH ₃ —H	419.0	414.5	417±2
CH ₃ CH ₂ —H	421.9	417.0	420–421
(CH ₃) ₃ C—H	412.1	406.8	413.1
Cyclopropane	419.6	413.3	411.5
Cyclobutane	415.5	411.5	417.4
Cyclopentane	414.0	409.1	416.1
Bicyclo[1.1.1]pentane-H(1)	409.4	407.5	411±3.5
Bicyclo[2.2.1]heptane-H(1)	411.3	409.0	
Cubane	407.6	406.5	404±3

a. R. R. Sauers, *Tetrahedron*, **55**, 10013 (1999).

TOPIC 3.1
Acidity of Hydrocarbons

basis of qualitative considerations of the orbital occupied by the unshared electron pair. In a planar carbanion, the lone pair occupies a *p* orbital. In a pyramidal geometry, the orbital has substantial *s* character. Since the electron pair has lower energy in an orbital with some *s* character, it would be predicted that a pyramidal geometry would be favored.

An effort has been made to dissect the substituent effects in carbanions into their component parts. The energy of the anion was calculated before and after allowing first electronic and then nuclear relaxation. This might be expected to roughly correspond to polar and resonance components, since the nuclear relaxation established the optimal geometry for delocalization (although there may be partial delocalization in the unrelaxed anion). The results are summarized in Table 3.40. Most of the energy change was found at the electronic relaxation stage, but substituents such as formyl and nitro, for which resonance delocalization is expected to be important, showed the largest effect of nuclear relaxation. Interestingly, the cyano group showed only a small nuclear relaxation component, suggesting that its anion-stabilizing effect is mainly of polar origin.

Tupitsyn and co-workers examined several series of hydrocarbons in an effort to confirm the importance of delocalization and hybridization changes as the major factors

Table 3.40. Electronic and Nuclear Relaxation Components of Carbanion Stabilization^a

Substituent	Electronic (kcal/mol)	Nuclear (kcal/mol)
H	67.8	0
NH ₂	61.9	1.0
OH	60.2	1.8
F	61.4	1.6
Cl	59.7	2.6
CH=O	64.5	5.9
C≡N	62.6	1.2
NO ₂	59.5	10.6
CH ₃ S	65.9	0.7
CH ₃ SO	62.6	2.7
CH ₃ SO ₂	60.0	1.4

a. F. Tupitsyn, A. S. Popov, and N. N. Zatssepina, *Russ. J. Gen. Chem.*, **68**, 1314 (1998).

in C–H acidity.¹⁸⁴ Acidity was estimated by using AM1 computations, calibrated to experimental deprotonation energies. For small-ring, bicyclic, and cage compounds, a correlation was found for the ΔE for deprotonation and the ^1H - ^{13}C coupling constant:

$$\Delta E_{\text{deprot}} = 1870(\text{kJ}) - 0.93 J_{\text{H}-\text{C}}$$

A similar correlation pertains to cyclic alkenes and dienes in which the deprotonation is from an sp^2 carbon:

$$\Delta E_{\text{deprot}} = 1867(\text{kJ}) - 1.05 J_{\text{H}-\text{C}}$$

These correlations suggest that the dominant factor for these compounds is the hybridization of the C–H undergoing deprotonation. For hydrocarbons for which delocalization is expected to be the major factor, e.g., toluene and diphenylmethane, a different kind of correlation was found:

$$\Delta E_{\text{deprot}} = 1640(\text{kJ}) - 0.70 \Delta E_{\text{relax}}$$

where ΔE_{relax} is the stabilization found when the carbanion constrained to the geometry of the original structure is allowed to relax to the minimum energy structure. These results support the idea that C–H acidity depends primarily on hybridization and anion stabilization. In addition to the hydrocarbons that show correlations with one of the two factors, some hydrocarbons are correlated by equations that contain terms both terms.

General References

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Problems

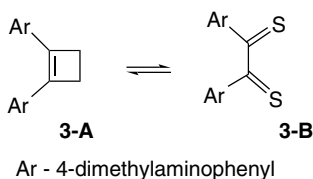
(References for these problems will be found on page 1158.)

3.1. Use thermochemical relationships to obtain the requested information.

- a. The ΔH_f of cyclohexane, cyclohexene, and benzene are, respectively, -29.5 , -1.1 , and $+18.9$ kcal/mol. Use this information to estimate the resonance stabilization of benzene.

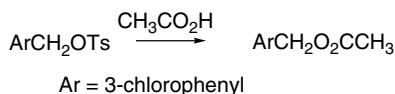
¹⁸⁴. I. F. Tupitsyn, A. S. Popov, and N. N. Satsepina, *Russian J. Gen. Chem.*, **67**, 379 (1997).

- b. Calculate ΔH for the air oxidation of benzaldehyde to benzoic acid, given that the ΔH_f of benzaldehyde and benzoic acid are -8.8 and -70.1 kcal/mol, respectively.
- c. Using the appropriate heats of formation from Table 3.1, calculate the heat of hydrogenation ΔH_{H_2} for 2-methyl-1-pentene.
- 3.2. Addition of methylmagnesium bromide to 2-methylcyclohexanone, followed by iodine-catalyzed dehydration of the resulting alcohol gave three alkenes in the ratio A:B:C = 3:31:66. Each alkene gave a mixture of *cis*- and *trans*-1,2-dimethylcyclohexane upon catalytic hydrogenation. When the alkene mixture was heated with a small amount of sulfuric acid, the ratio of A:B:C changed to 0.0:15:85. Assign structures to A, B, and C.
- 3.3. Measurement of the equilibrium constant for the interconversion of the dithiete **3-A** and the dithione **3-B** at several temperatures gave the data below. Calculate ΔG , ΔH , and ΔS .



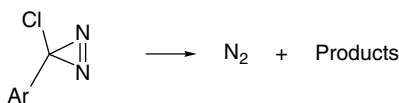
Temperature ($^{\circ}\text{C}$)	K
-2.9	16.9
11.8	11.0
18.1	8.4
21.9	7.9
29.3	6.5
32.0	6.1
34.9	5.7
37.2	5.3
42.5	4.6

- 3.4 a. Calculate the activation parameters (ΔH^{\ddagger} and ΔS^{\ddagger}) at 40°C for the acetolysis of 3-chlorobenzyl tosylate from the data given below:



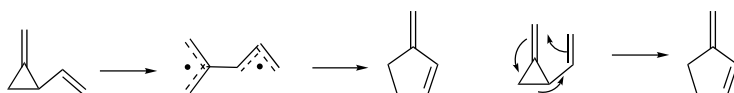
Temperature ($^{\circ}\text{C}$)	$k \times 10^5 \text{ s}^{-1}$
25.0	0.0136
40.0	0.085
50.1	0.272
58.8	0.726

- b. Calculate the activation parameters (E_a , ΔH^\ddagger , and ΔS^\ddagger) at 100°C from the data given for the reaction below.

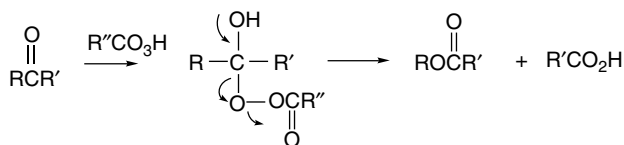


Temperature (°C)	$k \times 10^4 \text{ s}^{-1}$
60.0	0.30
70.0	0.97
75.0	1.79
80.0	3.09
90.0	8.92
95.0	15.90

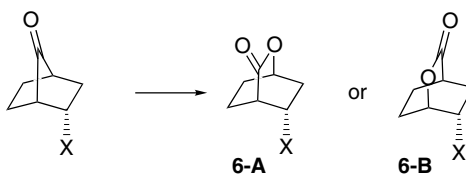
- 3.5. 2-Vinylmethylenecyclopropane rearranges thermally to 3-methylenecyclopentene. In the gas phase, the E_a is 26.0 kcal/mol, which is close to the estimated energy required for rupture of the C(2)–C(3) bond. Two possible mechanisms for this rearrangement are:



- Sketch qualitative reaction energy profiles for each process, based on the information given.
 - How might an isotopic labeling experiment distinguish between these mechanisms?
- 3.6. The Baeyer-Villiger oxidation of ketones to esters (or lactones) occurs by the following mechanism:

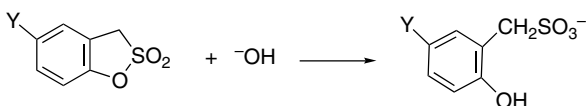


For *endo*-substituted bicyclo[2.2.1]heptan-7-ones, the product ratios shown below are observed. Account for the effect of the substituents.



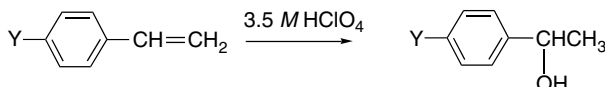
X	6A:6B
CN	100:0
CO ₂ CH ₃	77:23
Ph	51:49
<i>p</i> -NO ₂ Ph	75:25
<i>p</i> -FPh	52:48
<i>p</i> -CH ₃ OPh	39:61

- 3.7 a. Create Hammett plots versus σ and σ^- for the reaction shown below from the data given. Determine the value of ρ and compare the correlation with the two sets of substituent constants.



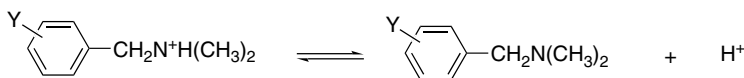
Y	$k M^{-1} s^{-1}$
H	37.4
CH ₃ O	21.3
CH ₃	24.0
Br	95.1
NO ₂	1430

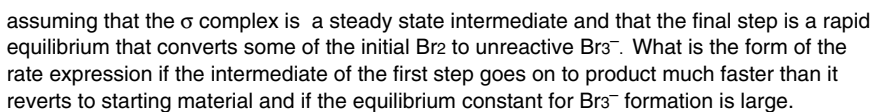
- b. The pseudo-first order rate constants for acid-catalyzed hydration of substituted styrenes in 3.5M HClO₄ at 25° C are given. Plot the data against σ and σ^+ and determine ρ and ρ^+ . Interpret the significance of the results.

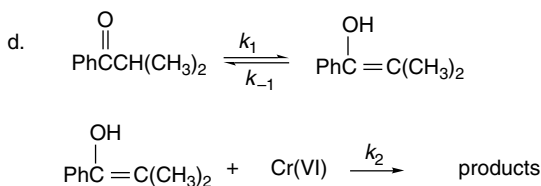


Y	$k \times 10^8 s^{-1}$
4-CH ₃ O	488,000
4-CH ₃	16,400
H	811
4-Cl	318
4-NO ₂	1.44

- c. The acidity of a series of substituted benzyldimethylammonium ions has been measured. Determine whether these data are correlated by the Hammett equation using σ and σ^+ . What is the value of ρ ? What interpretation do you put on its sign and magnitude?





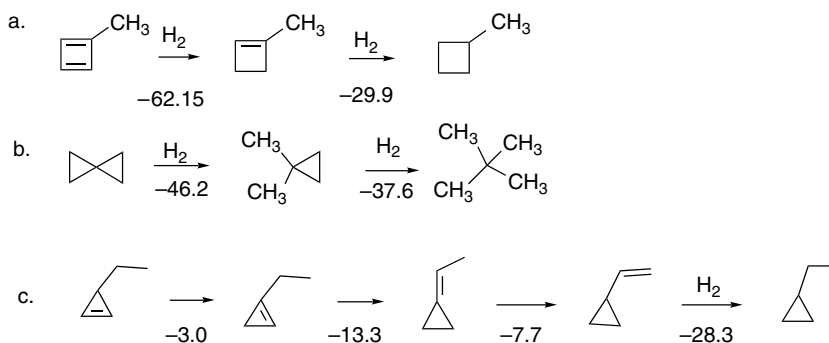


making no assumptions about the relative magnitude of k_1 , k_{-1} , or k_2 .

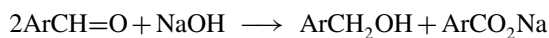
- 3.9. One method of estimating “aromatic stabilization” is to compare the heats of hydrogenation of cyclic conjugated systems with an acyclic molecule having the same number of conjugated bonds and π electrons. The table below gives the AM1 calculated heat of hydrogenation for various cyclic conjugated systems and for the corresponding polyene [ΔH_{H_2} (ref.)] For example, for benzene the comparison would be with 1,3,5-hexatriene. Calculate the aromatic stabilization or antiaromatic destabilization for each system. What conclusions do you draw? Relate your conclusions to HMO theory in Chapter 1. How does this computation deal with “strain?”

System	ΔH_{H_2} (ref.)	ΔH_{H_2} (cyclic system)
Cyclopropenyl cation	-13.3	10.6
Cyclopropenyl anion	4.7	-59.6
Cyclobutadiene	-50.7	-101.9
Cyclopentadienyl cation	-19.4	-72.9
Cyclopentadienyl anion	-0.3	-2.9
Benzene	-72.2	-45.0
Cycloheptatrienyl cation	-31.4	-23.9
Cycloheptatrienyl anion	-11.4	-26.4

- 3.10. A number of experimentally inaccessible ΔH values have been computed at the G2(MP2) level and are given below in kcal/mol. Taking for comparison ΔH_{H_2} of ethene as -32.4 kcal/mol, of 1-butene as -30.3 kcal/mol, and of cyclopropane to propane as -38.6 kcal/mol, indicate what factors lead to the observed differences in each step of the sequences shown.



- 3.11. The Cannizzaro reaction is a disproportionation that takes place in strongly basic solution and converts aromatic aldehydes to the corresponding benzyl alcohol and sodium benzoate.

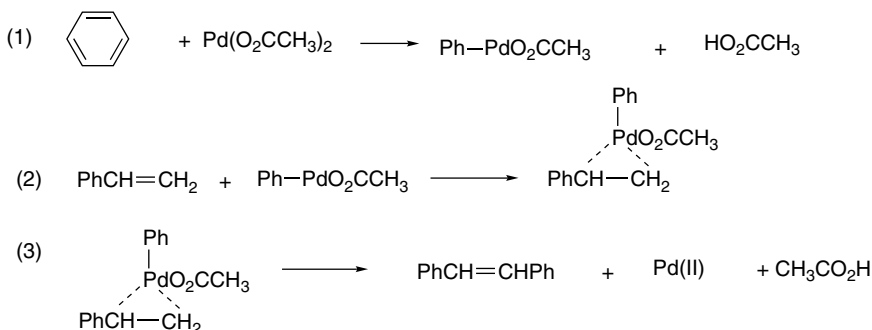


Several mechanisms, all of which involve a hydride transfer as a key step, have been postulated. On the basis of the following information, formulate one or more mechanisms that would be consistent with all the data provided. Indicate the significance of each observation with respect to the mechanism(s) you postulate.

1. When the reaction is carried out in D_2O , the benzyl alcohol contains no deuterium in the methylene group.
2. When the reaction is carried out in $H_2^{18}O$, both the benzyl alcohol and sodium benzoate contain ^{18}O .
3. The overall reaction rate is given by the expression

$$\text{Rate} = k_{\text{obs}}[\text{PhCH=O}]^2[{}^-\text{OH}]$$

4. The rates of substituted benzaldehydes are correlated by a Hammett LFER with $\rho = +3.76$.
 5. The solvent isotope effect $k_{D_2O}/k_{H_2O} = 1.90$
- 3.12. A mechanism for alkene arylation catalyzed by Pd(II) is outlined below. The isotope effect k_H/k_D was found to be 5 when benzene- d_6 was used. There was no isotope effect when styrene- β - d_2 was used. Which steps in the reaction mechanism could be rate determining, given this information on isotope effects?



- 3.13. Comparison of the gas phase acidity of substituted benzoic acids with pK_a values in aqueous solutions reveals some interesting comparisons.
1. The trend in acidity as a function of substituent is the same for both gas phase and aqueous solution, but the substituent effects are much stronger in the gas phase. (The $\Delta\Delta G$ for any given substituent is about 10 times larger in the gas phase.)
 2. Whereas acetic and benzoic acid are of comparable acidity in water, benzoic acid is considerably more acidic in the gas phase. (pK_a values are 4.75 and 4.19, respectively; and ΔG of ionization is 8.6 kcal/mol more positive for acetic acid.)
 3. While the substituent effect in the gas phase is nearly entirely an enthalpy effect, it is found that in solution, the substituent effect is largely due to changes in ΔS .

Discuss how difference between the gas phase and solution can cause these effects.

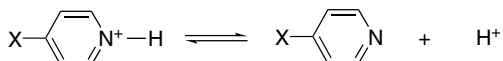
- 3.14. It has been found that the ^{13}C chemical shift of aromatic ring carbons are a good indicator of the intrinsic electron-releasing or electron-withdrawing capacity of substituents, without any perturbation from approaching reagents. Such perturbation is always present when substituent effects are measured on the basis of

reactivity. The changes in chemical shifts of C(4) in some substituted benzenes are given below. Plot these against σ , σ^+ , and σ^- . What conclusions do you draw from these plots in regard to the mix of resonance and polar components in each of the σ values?

X	$\Delta\delta^a$	X	$\Delta\delta^a$
NH ₂	-9.86	CF ₃	3.29
CH ₃ O	-7.75	CN	3.80
F	-4.49	CH ₃ CO	4.18
Cl	-2.05	CH ₃ O ₂ C	4.12
Br	-1.62	CH ₃ SO ₂	4.64
CH ₃	-2.89	NO ₂	5.53

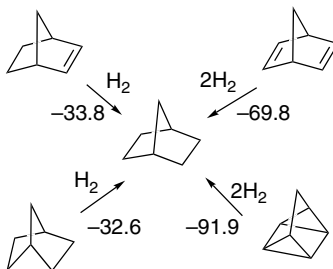
a. $\delta\Delta$ is the change in chemical shift in ppm relative to benzene in CCl₄ solution.

- 3.15. The ionization constants (pK_a) of 4-substituted pyridines have been measured, as have the ΔH of ionization at 25° C. Calculate ΔS for each ionization. Compare the contribution of ΔH and ΔS to the free energy of ionization. Test the data for linear free-energy correlations. Are the LFER dominated by the ΔH or ΔS term?



X	pK_a	ΔH (kcal/mol)	X	pK_a	ΔH (kcal/mol)
H	5.21	4.8	Cl	3.83	3.6
NH ₂	9.12	11.3	Br	3.75	3.5
CH ₃ O	6.58	6.8	CN	1.86	1.3
CH ₃	6.03	6.1			

- 3.16 a. Norbornene, norbornadiene, nortricyclane, and quadricyclane can all be hydrogenated to norbornane. The heats of hydrogenation are given in the chart. These data allow calculation of ΔH_f for the other derivatives and the results are given as Exp. in the table. The table also gives ΔH_f values calculated for each compound by MM and three semiempirical MO methods. Compare the accuracy of the semiempirical methods in predicting the experimental heats of formation.



Heats of Hydrogenation in kcal/mol

Calculated Enthalpies of Formation of Norbornane Analogs^a

Compound	MM ^b	MNDO	AM1	PM3	Exp.
Norbornadiene	55.5(30.9)	62.7	67.7	58.8	57.4
Norbornene	19.5(22.7)	25.3	26.0	22.0	21.4
Norbornane	-12.8(18.1)	-10.4	-14.4	-13.7	-12.4
Nortricyclane	19.5(52.6)	27.1	33.8	26.0	20.2
Quadricyclane	79.4(108.1)	79.1	104.4	86.3	79.5

a. In kcal/mol.

b. The calculated strain energies are given in parentheses.

- b. Subsequently, the same compounds were computed by ab initio and DFT methods. Isodesmic reactions were used to compare the ΔH_f of the compounds (except for G3(MP2), where atomization energies were used). Compare the ab initio and DFT results with the semiempirical results from Part (a).

Calculated Enthalpies of Formation of Norbornane Analogs^a

Compound	G2	G2(MP)	G2(MP2, SVP)G3(MP2)		B3LYP
Norbornadiene	56.3	57.0	56.0	56.0	66.5
Norbornene	18.5	19.1	18.0	18.5	28.9
Norbornane	−14.1	−13.6	−14.7	−13.8	−3.2
Nortricyclane	16.2	16.9	15.5	16.9	24.8
Quadricyclane	79.2	80.1	80.1	80.4	83.7

a. In kcal/mol.

- c. Heats of hydrogenation have also been calculated from the semiempirical data. Since the heats of hydrogenation include the ΔH_f of H₂, which is zero, they can be calculated as follows:

$$\Delta H_{H_2} = \Delta H_{f\text{product}} - \Delta H_{f\text{reactant}}$$

This leads to the calculated ΔH_{H_2} shown below. The ΔH_{H_2} can also be calculated on a strain compensation basis:

$$\Delta H_{H_2} = \Delta H_{f\text{product}} - \Delta H_{f\text{reactant}} + \text{strain relief}$$

The calculated values are included in the table. Compare the calculated and experimental results.

Calculated Calculated Heats of Hydrogenation of Norbornane Analogs^a

Compound	MM ^b	MNDO	AM1	PM3	Exp.
Norbornadiene	-68.3(1.5)	-73.1(-3.3)	-82.1(-12.3)	-72.5(-2.7)	-69.8
Norbornene	-32.3(1.5)	-35.7(-1.9)	-40.4(-6.6)	-35.7(-1.9)	-33.8
Nortricyclane	-32.3(0.3)	-37.5(-4.9)	-48.2(-15.6)	-33.7(-1.1)	-32.6
Quadricyclane	-92.2(-0.3)	-89.5(2.4)	-118.8(-26.9)	-100.0(-8.1)	-91.9

a. The numbers in parenthesis are the difference with the experimental value on a strain-compensated basis.

- 3.17. The second-order rate constants for the reaction of a number of amines with benzyl chloride are tabulated below. Calculate ΔH^\ddagger and ΔS^\ddagger from the data.

Compare the reactivity of the various amines. What trends and correlations between reactivity and ΔH^\ddagger do you note?

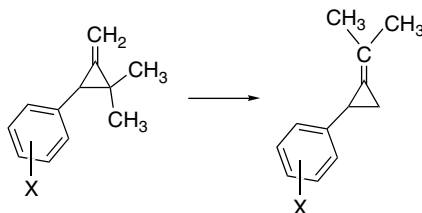
Rate Constants for the Reaction of Tertiary Amines with Benzyl Chloride

Amine	Rate constants $10^5 k_2 (M^{-1} s^{-1})$								
	20° C	24° C	30° C	40° C	50° C	60° C	70° C	80° C	90° C
(CH ₃) ₃ N	38.2	50.2	72.8						
(C ₂ H ₅) ₃ N				1.67	3.07	4.54	7.49		
(C ₃ H ₇) ₃ N				0.354	0.633	1.05	1.76	3.04	
(C ₄ H ₉) ₃ N				0.471	0.844	1.24	1.94	3.22	
(C ₆ H ₁₃) ₃ N				0.290	0.566	0.860	1.54	2.62	
(C ₈ H ₁₇) ₃ N				0.336	0.570	0.912	1.60	2.73	
PhN(CH ₃) ₂						0.135	0.233	0.384	0.698
Pyridine				0.168	0.337	0.910	1.55	2.63	
Quinoline					0.051	0.105	0.226	0.457	0.820

3.18. Some data are given below for both gas phase (ΔG) and DMSO (pK) acidity of substituted toluenes, phenylacetonitriles, and phenylmalononitriles that illustrate the strongly acidifying effect of the cyano substituent. For each series, plot ΔG versus pK . Do the plots show any evidence of a solvent attenuation effect; that is, do the substituent effects appear to be weaker in DMSO than in the gas phase?

Group	σ	Toluenes		Phenylacetonitriles		Phenylmalononitriles	
		ΔG_{gas}	pK	ΔG_{gas}	pK	ΔG_{gas}	pK
H	0.0	373.7	43.0	344.1	21.9	314.3	4.24
4-NO ₂	0.78	345.2	20.4	323.3	12.3	299.5	-1.8
3-NO ₂	0.71	355.7	33.5	330.9	18.1	303.0	1.7
4-CN	0.66	353.6	30.7	327.9	16.0		
3-CN	0.56			332.3	18.7	304.4	2.2
4-SO ₂ CF ₃	0.96	340.7	24.1				
4-SO ₂ Ph		352.1	29.8				
4-SO ₂ CH ₃	0.72	359.3					
4-PhCO	0.43	353.5	26.8				
4-CH ₃ CO	0.50	354.9					
4-CF ₃ CO	0.80	344.1					
4-CH ₃ O ₂ C	0.45	355.4					
4-(CH ₃) ₂ NCO	0.36	367.0					
4-CF ₃	0.54			332.9	18.1		
3-CF ₃	0.43			335.3	19.2		
4-Cl	0.23			338.5	20.5	309.0	3.14
3-Cl	0.37			337.5	19.5	308.8	2.7
4-F	0.06			342.4	22.2		
3-F	0.34			344.0	20.0		
4-CH ₃ O	-0.27			345.0	23.8	315.4	5.68
3-CH ₃ O	0.12			342.8			
4-CH ₃	-0.17			345.0	22.9	315.7	4.85
3-CH ₃	-0.07			344.2			
4-(CH ₃) ₂ N	-0.83			346.6	24.6		

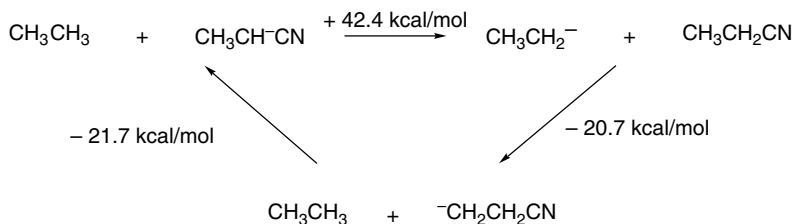
- 3.19. The rate of thermal rearrangement of 3-aryl-2,2-dimethylmethylenecyclopropanes has been studied as a function of aryl substituents. Some of the data are given below. Examine the rate data for correlation with the Hammett σ -substituent constants. What conclusion do you draw about the mechanism?



Substituent	$10^4 k s^{-1}$	Substituent	$10^4 k s^{-1}$
4-(CH ₃) ₂ N	28.2 ^a	3-CH ₃ O	3.40
4-CH ₂ =CH	16.7 ^a	3-Cl	3.30
4-NO ₂	13.5 ^a	3-F	3.17
4-CN	10.28	3-CF ₃	3.08
4-Ph	10.3 ^a	4-F	2.98
4-CH ₃ S	9.53	3-NO ₂	2.76 ^a
4-CO ₂ CH ₃	8.09	3-CN	2.69
4-CH ₃ O	6.16		
4-(CH ₃) ₃ Si	5.24		
4-Br	4.88		
4-(CH ₃) ₃ C	4.78		
4-Cl	4.75		
4-CH ₃	4.65		
4-CF ₃	4.25		
3-(CH ₃) ₃ Si	3.87		
3-CH ₃	3.82		
H	3.58		

a. Calculated from relative rate at 80° C in benzene.

- 3.20. The series of isodesmic reactions shown below has been calculated at the MP2/aug-cc-PVDZ level. The results are in good agreement with experimental gas phase proton affinity data.

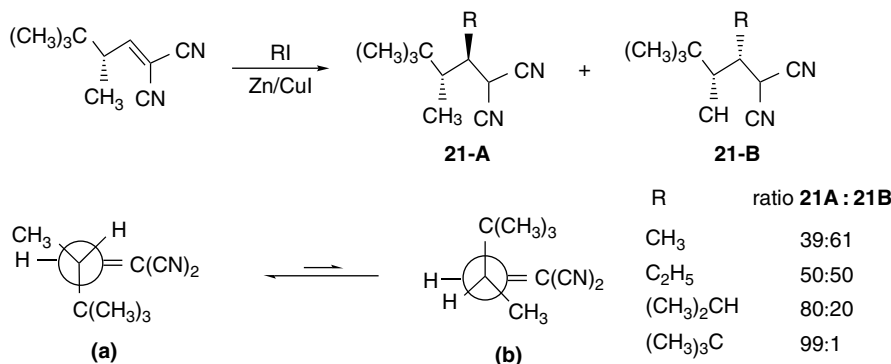


Data are also available for the pK_a of mono-, di-, and tri-cyanomethane. These data suggest substantially less cumulative drop-off as compared to an acetyl substituent. The first acetyl group causes a substantially *larger* increase in acidity, whereas the second acetyl has a *smaller* effect.

	CH ₄	CH ₃ CN	CH ₂ (CN) ₂	CH(CN) ₃	$\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_3$	$\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\overset{\text{O}}{\parallel}\text{CCH}_3$
p <i>K</i>	49.6	29.4	11.7	-5.1	19.3	8.9

β -Cyano substituents also have a quite strong acidifying effect. A value of 29 ± 6 kcal/mol has been estimated, as compared to 42 kcal/mol for α -cyano. Structural computations find a shortening of the C(α)-CN bond in α -cyanoethyl anion but a lengthening of the C(β)-CN bond in the β -cyanoethyl anion. What structural features of the CN might contribute to its anion stabilizing capacity, as compared with other EWG substituents such as acetyl.

- 3.21. The diastereoselectivity of alkyl radical addition to substituted alkylidene malononitriles is a function of the size of the attacking radical when there is a bulky substituent at the γ -carbon. Conformational analysis of the reactant indicates that it prefers conformation **a** over **b** by 3.0 kcal/mol. Suggest a TS structure, showing reactant conformation and reagent trajectory that is in accord with these results. Use the Curtin-Hammet principle (p. 296) to construct a reaction energy diagram that illustrates the product composition in terms of TS energy.



- 3.22. In the interpretation of substituent effects, consideration must be given as to whether the effect is primarily on the reactant or the product. Some data pertaining to the changes in some substituted benzoic acids, derived from PM3 computations, are given below. The calculated $\delta\Delta H$ for ionization in the gas phase is given, as are the charges of the H, CO₂H, and CO₂⁻ groups and the energy of the anion HOMO. Construct correlation plots of $\delta\Delta H$ with each of the structural properties and also against the values of σ_m and σ_p from Table 3.26. What conclusions do you draw about the effects of substituents on H, CO₂H, and CO₂⁻, and how would these results be reflected in relative acidity?

Substituent	$\delta\Delta H$	q_H	$q_{\text{CO}_2\text{H}}$	$q_{\text{CO}_2^-}$	HOMO _(anion) (eV)
H	0	0.229	-0.0503	-1.237	-4.4549
4-F	-3.68	0.231	-0.0436	-1.229	-4.6395
3-F	-4.02	0.231	-0.0415	-1.224	-4.6487

(Continued)

Substituent	$\delta\Delta H$	qH	qCO_2H	qCO_2^-	HOMO _(anion) (eV)
4-Cl	-3.11	0.230	-0.0460	-1.227	-4.6383
3-Cl	-3.10	0.230	-0.0440	-1.226	-4.6323
4-CN	-7.95	0.232	-0.0385	-1.215	-4.8765
3-CN	-7.49	0.232	-0.0368	-1.217	-4.8451
4-NO ₂	-12.98	0.234	-0.0297	-1.199	-5.1198
3-NO ₂	-11.14	0.235	-0.0277	-1.207	-5.0247
4-CH ₃	+0.44	0.228	-0.0519	-1.237	-4.4563
3-CH ₃	+0.22	0.228	-0.0514	-1.237	-4.4585
4-OCH ₃	+0.15	0.228	-0.0520	-1.237	-4.5000
3-OCH ₃	-0.36	0.228	-0.0490	-1.230	-4.5047

- 3.23. From the kinetic data below, calculate ΔH^* and ΔS^* for each nucleophilic substitution reaction with *n*-butyl tosylate in methanol and DMSO. What trends do you note in ΔH^* and how would you explain them? What trends do you note in ΔS^* and how would you explain them?

Nucleophile	Solvent	Second-order rate constants (in mol ⁻¹ s ⁻¹ × 10 ⁴) at °C			
		k_{20}	k_{30}	k_{40}	k_{50}
Cl ⁻	DMSO	5.06	16.7	50.4	
	MeOH	0.00550	0.0226	0.0852	
N ₃ ⁻	DMSO	16.1	48.3	135	
	MeOH	0.152	0.514	1.66	
Br ⁻	DMSO	1.75	5.69	17.8	
	MeOH	0.0191	0.0721	0.250	
SCN ⁻	DMSO	0.115	0.365	1.11	
	MeOH	0.0512	0.165	0.481	
I ⁻	DMSO		1.75	5.50	16.0
	MeOH	0.0767	0.275	0.956	

- 3.24. Use the computed values of H_{298} (in Hartrees) from the reference set below to construct homo desmotic reactions and calculate the stabilization or destabilization (strain) of the following molecules.

- 1,3,5,7-Cyclooctatetraene, $H_{298} = -308.96286$
- Bicyclo[1.1.0]butane, $H_{298} = -155.62203$
- Tetracyclo[3.2.0.0^{4,9}.0^{6,8}]heptane (Quadricyclane), $H_{298} = -567.74092$

Reference Data^a

CH ₄	-40.40707	CH ₂ =CH ₂	-78.41192	<i>c</i> -C ₃ H ₆	-116.37701
C ₂ H ₆	-79.62641	CH ₃ CH=CH ₂	-117.63998	<i>c</i> -C ₄ H ₈	-156.85340
C ₃ H ₈	-118.85022	CH ₂ =C=CH ₂	-116.41308	C ₆ H ₆	-231.77508
C ₄ H ₁₀	-158.07430	(CH ₃) ₂ C=CH ₂	-156.86995		
<i>i</i> -C ₄ H ₁₀	-158.07751	CH ₂ =CHCH=CH ₂	-155.65855		

a. L. A. Curtiss, K. Raghavachari, P. C. Refern, and J. A. Pople, *J. Chem. Phys.*, **106**, 1063 (1997)



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